Request for permission for oral testimony at Idaho Medicaid's P&T Committee meeting on 04-15-2011

Submission # 6

The following request has been:

- ○ Approved
- ☒ Denied

Gennrich, Jane - Medicaid

From: Paul J Setlak [paul.setlak@abbott.com]
Sent: Monday, March 14, 2011 5:39 PM
To: Gennrich, Jane - Medicaid; Eide, Tamara J. - Medicaid
Subject: Idaho Medicaid P&T Committee Request - Creon
Attachments: WWhitcomb, et al 2010.pdf; Kuhn, et al 2010.pdf; Graff, et al - B - 2010.pdf; Graff, et al 2010.pdf

March 14, 2011

Pharmacy & Therapeutics Committee
Attention: Tami Eide, Pharm.D.
3232 Elder Street
Boise, Idaho 83705

Dear Dr. Eide:

Thank you for your unsolicited request for updated clinical information on Creon®. Please find enclosed updated clinical information for the product being reviewed, per your direction found on the website (http://healthandwelfare.idaho.gov/Medical/PrescriptionDrugs/PTCommittee/tabid/207/Default.aspx), for consideration as part of the upcoming State of Idaho P&T Committee Drug Review Meeting to be held April 15, 2011.

Creon®

1. Graff GR, Maguiness K, McNamara J, Morton R, Boyd D, Beckmann K, Bennett D. Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged 7 to 11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. *Clin Ther.* 2010;32(1):89-103.
2. Whitcomb DC, Lehman GA, Vasileva G, Malecka-Panas E, Gubergrits N, Shen Y, Sander-Struckmeier S, Caras S. Pancrelipase Delayed-Release Capsules (CREON) for Exocrine Pancreatic Insufficiency due to Chronic Pancreatitis or Pancreatic Surgery: A Double-Blind Randomized Trial. *Am J Gastroenterol.* 2010 May 25. [Epub ahead of print, PMID: 20502447]
3. Graff GR, McNamara J, Royall J, Caras S, Forssmann K. Safety and tolerability of a new formulation of pancrelipase delayed-release capsules (CREON) in children under seven years of age with exocrine pancreatic insufficiency due to cystic fibrosis: an open-label, multicentre, single-treatment-arm study. *Clin Drug Investig.* 2010;30(6):351-64
4. Kuhn RJ, Gelrud A, Munck A, Caras S. CREON (Pancrelipase Delayed-Release Capsules) for the treatment of exocrine pancreatic insufficiency. *Adv Ther.* 2010 Dec;27(12):895-916.

For full prescribing information, please see the most up to date package insert located at:
Creon®: http://rxabbott.com/pdf/creon_PI.pdf
Additionally, based on the State of daho promulgated rules regarding "(3) new studies released since the last review," please permit this correspondence to also serve as a request to provide oral presentation based on the clinical updates provided.

Please understand that this information is intended to provide only a clinical update of Creon®. If you would like additional information or have more questions please contact me at 773-320-7057.

Thank you and have a wonderful day.

Sincerely,
Dr. Paul Setlak

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A Promise for Life

Pancrelipase Delayed-Release Capsules (CREON) for Exocrine Pancreatic Insufficiency due to Chronic Pancreatitis or Pancreatic Surgery: A Double-Blind Randomized Trial

David C. Whitcomb, MD, PhD[1], Glen A. Lehman, MD[2], Galina Vasileva, MD[3], Ewa Malecka-Panas, MD, PhD[4], Natalya Gubergrits, MD, PhD, DSc[5], Yannan Shen, MS[6], Suntje Sander-Struckmeier, PhD[7] and Steven Caras, MD, PhD[6]

OBJECTIVES: **Pancreatic-enzyme replacement therapy (PERT) is the standard of care to prevent maldigestion, malnutrition, and excessive weight loss in patients with exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (CP) or pancreatic surgery (PS). Our objective was to assess the efficacy and safety of a new formulation of pancrelipase (pancreatin) delayed-release 12,000-lipase unit capsules (CREON) in patients with EPI due to CP or PS.**

METHODS: **This was a double-blind, randomized, multicountry, placebo-controlled, parallel-group trial enrolling patients ≥18 years old with confirmed EPI due to CP or PS conducted in clinical research centers or hospitals. After a 5-day placebo run-in period (baseline), patients were randomized to pancrelipase (72,000 lipase units per meal; 36,000 per snack) or placebo for 7 days. All patients received an individually designed diet to provide at least 100 g of fat per day. The primary efficacy measure was the change in coefficient of fat absorption (CFA) from baseline to end of the double-blind period, analyzed using non-parametric analysis of covariance. Secondary outcomes included the coefficient of nitrogen absorption (CNA), clinical symptoms, and safety parameters.**

RESULTS: **In total, 25 patients (median age of 54 years, 76% male) received pancrelipase and 29 patients (median age of 50 years, 69% male) received placebo. The mean ± s.d. change from baseline in CFA was significantly greater with pancrelipase vs. placebo: 32.1±18.5% vs. 8.8±12.5% (P<0.0001). Similarly, the mean ± s.d. change from baseline in CNA was greater for pancrelipase vs. placebo: 97.7±82.3% vs. 24.4±101.0% (P=0.0013). Greater improvements from baseline in stool frequency, stool consistency, abdominal pain, and flatulence were observed with pancrelipase vs. placebo. Treatment-emergent adverse events (TEAEs) were reported in five patients (20.0%) in the pancrelipase group and in six (20.7%) in the placebo group; the most common were gastrointestinal (GI) events and metabolism/nutrition disorders. There were no treatment discontinuations due to TEAEs.**

CONCLUSIONS: **Pancrelipase delayed-release 12,000-lipase unit capsules were effective in treating fat and nitrogen maldigestion with a TEAE rate similar to that of placebo in patients with EPI due to CP or PS.**

Am J Gastroenterol advance online publication, 25 May 2010; doi:10.1038/ajg.2010.201

INTRODUCTION

A primary function of the exocrine pancreas is to facilitate digestion of complex nutrients by synthesizing pancreatic lipase, pancreatic amylase, a variety of proteolytic zymogens, and other pro-enzymes and delivering them to the proximal small intestine to mix with chyme as it exits the stomach (1). Exocrine pancreatic insufficiency (EPI) describes a deficiency or absence of digestive enzymes leading to maldigestion of food and

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consequently malabsorption of nutrients. EPI occurs with acinar-cell dysfunction or destruction or blockage of the connection between the duct system and the intestine. Loss of pancreatic mass through surgical resection for benign or malignant diseases of the pancreas is also a common cause of EPI (2–4).

The most common cause of EPI in adults is chronic pancreatitis (CP), an inflammatory syndrome characterized by progressive and irreversible destruction of the pancreas (5,6). The clinical course of CP is highly variable and unpredictable, reflecting a complex interaction of multiple factors (7,8). This variability requires individualized treatment for patients as complications of CP arise or as glandular function deteriorates. Removal of the contributing factors (e.g., alcohol, smoking, and control of elevated triglyceride levels) may limit disease progression, although reversal and regeneration of the destroyed pancreas is not known to occur. Owing to the progressive nature of CP and the complexity of the symptomatology, the onset of EPI may be insidious, especially if the diet is variable or the patient has confounding factors such as alcoholism. Severe symptoms or complications may require surgical resection of the pancreas (including total pancreatectomy with islet-cell auto-transplantation), which further diminishes the capacity of the gland to produce digestive enzymes and worsens the EPI.

Pancreatic cancer, intraductal papillary mucinous neoplasm, mucinous cystic lesions with premalignant characteristics, and benign tumors of the pancreas are also major pancreatic diseases that may lead to EPI. The EPI may initially be caused by blockage of the pancreatic duct and may become irreversible with pancreatic surgery (PS), ranging from local resection to total pancreatectomy (2,9). For these conditions, the risk for EPI depends on the type and extent of surgery (2,4,10).

Less common conditions that result in EPI are also important. The majority of individuals with cystic fibrosis are affected by EPI (11). Traumatic injury to the pancreas and acute necrotizing pancreatitis may also result in EPI (12). Finally, failure of the acinar cells to produce digestive enzymes can occur in conditions that include Shwachman–Diamond syndrome, celiac disease, and inflammatory bowel disease, which also result in variable EPI (4).

The predominant symptoms of EPI-associated maldigestion include malnutrition, steatorrhea, diarrhea, abdominal pain, and weight loss (13). These clinical symptoms, and specifically steatorrhea, occur when pancreatic enzyme output falls below 10% of the normal levels (4,14,15), although this has been questioned by some investigators (16). Furthermore, clinically relevant maldigestion may occur earlier than the appearance of overt symptoms (17); there may be significant maldigestion and protein malnutrition in patients without the classic clinical sign of steatorrhea, which can be detected by more sensitive function testing and measurement of serum markers of nutrition (13,18). Protein/nitrogen absorption is not as well characterized as fat absorption in CP; however, improvement in protein absorption is expected to have nutritional benefits in patients with CP or after PS (10,18).

Effective management of EPI is necessary to prevent malnutrition and its long-term effects on health and to relieve symptoms that adversely affect patient's quality of life. The standard of care for treating maldigestion due to EPI regardless of etiology is pancreatic-enzyme replacement therapy (PERT). PERT is considered to be effective, safe, and well tolerated for EPI on the basis of a limited number of clinical trials in patients with CP, after PS, and in cystic fibrosis, and on extensive clinical experience (10,19–25). In addition to the treatment of maldigestion, PERT may also be useful in reducing pain in some patients with CP, particularly those with less advanced disease, although conflicting outcomes have been observed in controlled clinical trials, with some achieving pain relief with PERT and others not (5,26). In 2004, the United States Food and Drug Administration (FDA) released a mandate requiring new drug applications to be approved for all PERT products to ensure consistent quality, efficacy, and safety (27).

The current study was conducted to show superior efficacy of a new formulation of pancrelipase (pancreatin) delayed-release 12,000-lipase unit capsules (CREON, Solvay Pharmaceuticals Inc., Marietta, GA) over placebo in improving fat absorption in patients with EPI due to CP or PS; protein absorption, overall symptoms of maldigestion, safety, and tolerability were also assessed. This formulation was recently approved by the FDA for EPI and complies with the FDA mandate requirement for all PERT products to have lipase activity at 100% of the label claim. In addition, minor changes to the inactive ingredients of the capsule and the enteric coating were made in response to general FDA and European Union directives. The new formulation was shown to be safe and effective in treating EPI due to cystic fibrosis in patients ≥7 years of age when administered as 12,000- or 24,000-lipase unit capsules (28,29).

METHODS

Protocol

This double-blind, randomized, placebo-controlled, two-arm, parallel-group trial was designed to test the efficacy and safety of pancrelipase delayed-release capsules (clinicaltrials.gov registration number NCT00414908). The study was conducted in Bulgaria, Poland, Russia, Serbia, Ukraine, and the United States of America; 46 centers participated in the screening phase and 27 centers randomized patients to treatment. Data from an open label, long-term extension phase focusing on safety will be reported separately.

This study was conducted in compliance with applicable national regulations and with Good Clinical Practice, an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies which involve the participation of human patients that is consistent with the ethical principles originating in the Declaration of Helsinki. The protocol, including all substantial protocol amendments, was approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) at each site and written approval was obtained from the IRB/IEC before the study was implemented. All patients provided written informed consent before any study-related procedures were performed using an IRB/IEC-approved informed consent form. Written reports of the clinical study status were submitted by the investigator or sponsor to the IRB/IEC annually, or more frequently if requested, with the final study notification provided to the IRB/IEC within 90 days of study completion. Appropriate training and security measures were completed with the investigator and all authorized study-site personnel before the study was initiated and before any data were entered into the system for any study patients.

Patients

Patients ≥18 years of age who had provided written informed consent were eligible if they had confirmed CP or total or partial pancreatectomy >180 days before enrollment, and confirmed EPI. CP was to be proven (in medical history) radiographically or histologically by at least one of the following criteria: imaging techniques (ultrasound, computed tomography, magnetic resonance imaging, or endoscopic ultrasound); endoscopic retrograde cholangiopancreatography; plain film of the abdomen with pancreatic calcification; or histology.

EPI had to be proven by direct pancreatic function testing, e.g., abnormal-secretin test, or fecal elastase <100 μg/g, or fecal fat >15 g/day (according to 72-h fecal fat test), or total pancreatectomy documented in medical history. A fecal fat threshold of >15 g/day characterized patients with severe EPI who had a high probability of meeting the interim inclusion criteria and thus would be eligible for randomization to the double-blind phase. If medical records for a patient did not include documentation of the above, a fecal-elastase test was performed during screening to confirm subject eligibility (fecal elastase <100 μg/g required). Women with child-bearing potential were required to agree to use adequate birth control throughout the study and for 30 days after the last dose of study drug.

Exclusion criteria included severe medical conditions that might limit participation in or completion of the study, or recent (as per investigator's judgment) major surgery with the exception of appendectomy, PS for CP, abdominal surgery due to the underlying pancreatic disease that necessitated the surgery (e.g., pancreatectomy with additional abdominal surgery), or gall bladder removal. Also excluded were patients with ileus or acute abdomen, any type of malignancy in the digestive tract other than pancreatic cancer in the past 5 years, any type of malignancy not in remission, HIV, celiac disease, Crohn's disease, presence of a pancreatic pseudocyst ≥4 cm, continued excessive intake of alcohol or drug abuse, known allergy to pancrelipase (pancreatin) or the inactive ingredients of pancrelipase delayed-release capsules, or exposure to an experimental drug within 4 weeks of the start of the study.

Concomitant medications influencing duodendal pH (e.g., H2-receptor antagonists, antacids, sucralfate, proton pump inhibitors, prostaglandins, anti-cholinergic agents, or somatostatin), gastric emptying (e.g., metoclopramide, cisapride, or erythromycin), and bile secretion (e.g., bile acids, cholecystokinin antagonists) were permitted during the study provided they were administered at a stable dose. Any medications that could interfere with the study medication, such as other pancreatic enzyme preparations or antidiarrheals, were prohibited.

Assignment to treatment

This study comprised a single-blind placebo run-in period followed by a double-blind randomized period, after which eligible patients could enter a 6-month open-label extension phase (open-label data to be reported separately).

During both the run-in and randomized periods, all patients were actively monitored and treated in a strictly controlled inpatient setting such as a clinical research unit, clinic facility, or hospital. Site personnel monitored compliance with study procedures including dietary and stool collection requirements.

Patient enrollment was carried out by the investigators. The study design is shown in **Figure 1**. Following a pre-study screening assessment to confirm eligibility, patients entered a 5-day single-blind placebo run-in period (baseline), and received 24 placebo capsules orally per day consisting of six capsules per main meal (three meals daily) and three capsules per snack (two snacks daily). Following the single-blind placebo run-in period, patients were discharged from study centers for up to 16 days while their eligibility for randomization to the double-blind phase was assessed. During this time there were no restrictions regarding pancreatic supplementation therapy. Therefore patients could take their usual PERT and continue with their normal home diet. Patients who satisfied the following eligibility criteria were randomized to double-blind treatment with either pancrelipase or placebo: compliant with study procedures including diaries and stool collections, total stool fat content of ≥40 g, and coefficient of fat absorption (CFA) <80% during the run-in period. Patients eligible to enter the double-blind phase were randomized 1:1 to pancrelipase delayed-release capsules or placebo for 7 days, taken orally. Randomization was carried out centrally by telephone by the pharmaceutical supplies department of Solvay Pharmaceuticals, B.V. using blocks of pre-specified size and stratified by site. Patients in the pancrelipase group received 72,000 lipase units per main meal (six 12,000-lipase unit capsules) and 36,000 lipase units per snack (three 12,000-lipase unit capsules), to be taken during meals. Patients in the placebo group received placebo capsules as per the run-in period.

Masking

Study medication for the run-in and double-blind randomized periods was packaged in aluminum blister packs containing the required dose per meal or snack and packaged together as a daily supply. All study medication was provided in identical packaging with the same labeling, and the study drug and placebo capsule appearance was identical, to maintain blinding.

Efficacy assessments

Food consumed by each subject was planned in advance by the site dietitian in consultation with the subject to ensure consumption of at least 80 g of fat each day. To maintain this minimum level of intake on each day during both periods, the dietitian designed a daily diet containing at least 100 g of fat. All food during both treatment periods was provided to the subject by center personnel and compliance was determined daily.

A 72-h stool collection was carried out during the run-in period and at the end of the double-blind period to allow measurement

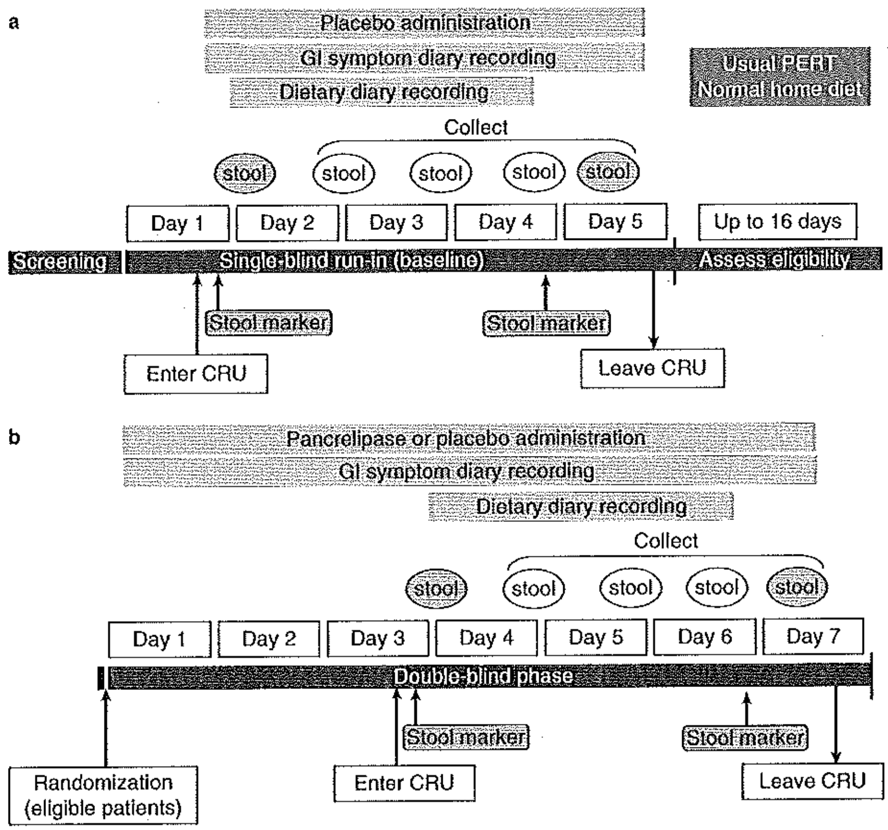

Figure 1. Study design for the (**a**) placebo run-in and (**b**) double-blind, randomized phase. CRU, clinical research unit; GI, gastrointestinal; PERT, pancreatic-enzyme replacement therapy.

of stool fat and stool nitrogen (**Figure 1**). To ensure accurate collection of stools, after entering the research unit, patients took one dose of blue food dye (500 mg FD&C Blue #2 indigo carmine, Brenntag GmbH, Mülheim an der Ruhr, Germany; Roha-Caleb UK Ltd, Caldicot, UK) to mark the beginning of each stool collection period (on day 1 of the run-in period; day 3 of the randomized period) and then a second dose 72 h later to mark the end of each stool collection period (on day 4 of the run-in period; day 6 of the randomized period). Compliance with stool collection requirements was monitored and recorded daily in the patients' gastrointestinal (GI) diaries by site personnel. Patients kept a daily GI symptom diary during the run-in and randomized periods and a dietary diary during both 72-h stool collection periods, beginning and ending with administration of the blue food dye; completion of the diaries was monitored by site personnel. Patients were released after passing the second blue-stool marker. At the discretion of the investigator, patients were allowed to return home or to a local hotel in the evening after their last meal with detailed instructions regarding food consumption and stool collection.

The primary outcome measure was the change in CFA from baseline to the end of the double-blind treatment period. The CFA was calculated from the fat intake and excretion according to the following equation:

$$\text{CFA (\%)} = 100\ ((\text{fat intake (g)} - \text{fat excretion (g)})/\text{fat intake (g)})$$

Stool fat and stool nitrogen were measured in a central laboratory according to the methods of van de Kamer (30,31) and Kjeldahl (32), respectively. Total daily fat intake and protein intake were determined from each subject's dietary diary for the 72-h stool collection period by a registered dietitian from the investigative site.

Secondary efficacy outcomes included the coefficient of nitrogen absorption (CNA), stool fat, stool nitrogen, and clinical symptomatology. The CNA was calculated according to the following equation:

$$\text{CNA (\%)} = 100\ ((\text{nitrogen intake (g)} - \text{nitrogen excretion (g)})/\text{nitrogen intake (g)})$$

Clinical symptomatology was assessed by the investigator by asking patients to provide information regarding stool frequency (number of stools per day), average stool consistency (0 = hard, 1 = formed/normal, 2 = soft, 3 = watery), average flatulence (0 = none, 1 = mild, 2 = moderate, 3 = severe), and average abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Safety evaluation

Safety measures included physical examination, assessment of vital signs, and safety laboratory values (hematology, biochemistry, and urinalysis), and recording of adverse events (AEs) according to the Medical Dictionary for Regulatory Activities version 8.1. AEs were considered treatment-emergent adverse events (TEAEs) if they had started during treatment, or if pre-existing AEs had worsened during treatment.

In accordance with the European Union Clinical Trial Directive, the study sponsor was to inform all participating IRB/IECs and national authorities of all serious AEs, serious adverse drug reactions, suspected and unexpected serious adverse drug reactions, or other safety-related information that occurred during the clinical study.

Statistics

Sample size was determined based on the primary efficacy end point (change from baseline in CFA). Using a two-sided t-test at a significance level of 0.05 and assuming an s.d. of 14%, 23 patients were required in each treatment group to detect a difference of 14% between pancrelipase and placebo at 90% statistical power. All efficacy analyses were performed on the full analysis sample, which included all patients who had at least one dose of study medication and for whom at least one post-baseline efficacy measurement was available. Safety analyses included all patients having at least one dose of study medication. All efficacy and safety variables for the double-blind period were summarized by standard descriptive methods.

The protocol required at least 66% of stool samples to be collected during the randomized period for inclusion in the analysis; if stool collection was less than 66%, the sample was considered invalid and was not analyzed. For the primary outcome measure, if missing stool samples occurred, fat excretion was imputed using individual subject fat-excretion values from the placebo run-in period provided that stool collection was at least 66%. The change from baseline in CFA and CNA was compared between treatment groups on the basis of a nonparametric analysis of covariance model including an effect for treatment and with the corresponding baseline value as a covariate (necessary assumptions were not met for parametric analysis of covariance). Three supporting analyses of CFA data were also carried out to assess the impact of (i) analysis of CFA data without imputed values, (ii) analysis of data from patients with 100% stool collection compliance in the randomized period, and (iii) per-protocol analysis excluding patients with protocol deviations.

For stool fat, stool nitrogen, and stool frequency, treatment comparisons were made on the basis of a parametric analysis of covariance model including an effect for treatment and with the corresponding baseline value as a covariate. For clinical symptomatology, P-values for treatment-group comparisons at each study visit were based on the χ^2-test; if cell sizes were too small, then P-values from Fisher's exact test were presented.

RESULTS

Participant flow and follow-up

In total, 180 patients provided consent, 179 entered the run-in period, and 54 were randomized (25 pancrelipase, 29 placebo) between 4 April 2007 and 18 August 2008. Overall, 52 patients completed the 1-week double-blind period (**Figure 2**). Patients completing the double-blind phase entered an open-label extension phase (data to be reported separately). A high proportion of patients were ineligible for the double-blind phase as they did not meet the strict interim inclusion criteria requirements for severe EPI of CFA <80% and/or stool fat excretion ≥40 g. Demographic characteristics were similar across the two treatment groups, as shown in **Table 1**. The proportion of patients with more severe

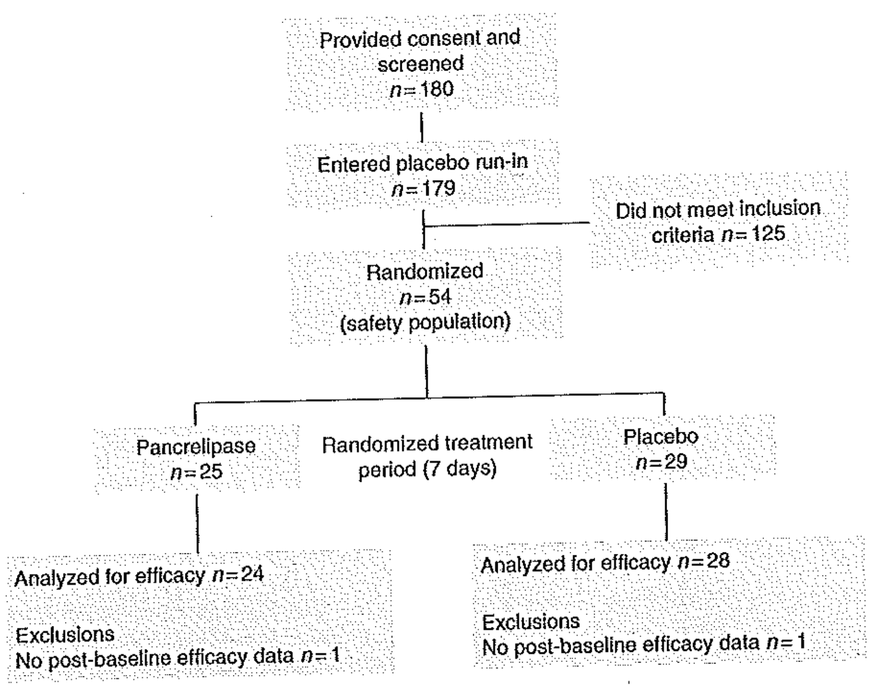

Figure 2. Patient disposition.

Table 1. Subject characteristics at baseline—safety sample

Parameter	Pancrelipase (n=25)	Placebo (n=29)
Age, years		
Mean±s.d.	52.0±9.6	50.5±7.7
Median (min/max)	54.0 (32/75)	50.0 (38/66)
Gender, n (%)		
Male	19 (76.0)	20 (69.0)
Female	6 (24.0)	9 (31.0)
BMI, kg/m²		
Mean±s.d.	23.4±4.4	22.2±4.4
Race, n (%)		
White	25 (100.0)	28 (96.6)
Black or African-American	0	1 (3.4)
Diagnosis, n (%)		
Chronic pancreatitis	16 (64.0)	24 (82.8)
Pancreatic surgery[a]	9 (36.0)	5 (17.2)
Duration of previous enzyme therapy, years		
Mean±s.d.	4.9±5.4	4.9±6.7
Baseline coefficient of fat absorption, n (%)[b]		
≤50 %	9 (36.0)	10 (35.7)
>50 %	16 (64.0)	18 (64.3)
Region		
United States	7 (28.0)	7 (24.1)
Eastern and Central Europe	18 (72.0)	22 (75.9)

BMI, body mass index; max, maximum; min, minimum.
[a]Includes partial and total pancreas removal.
[b]Data missing for one patient in the placebo group.

EPI (CFA ≤50%) was similar across the two treatment groups. However, the pancrelipase group contained a greater proportion of PS patients (36.0%) compared with the placebo group (17.2%). Only one patient had undergone PS for pancreatic malignancy; other cases of PS were due to CP. All patients were receiving PERT before the study-entry.

Mean treatment compliance (safety sample) in the pancrelipase and placebo groups was 96.4% and 95.5%, respectively, in the run-in period and 93.0% and 93.1%, respectively, during the randomized period.

The number of patients with protocol deviations was five in the pancrelipase group (one exclusion criteria (baseline CFA ≥80%) and stool collection, two stool collection, and two treatment compliance) and eight in the placebo group (one concomitant medication, four stool collection, and three treatment compliance).

During the double-blind phase, 9 patients (36%) in the pancrelipase group and 8 patients (28%) in the placebo group were taking proton pump inhibitors or H2-receptor antagonists at stable doses. No patients were taking octreotide.

Table 2. Mean±s.d. for the coefficient of fat absorption and for the coefficient of nitrogen absorption—full-analysis sample

	Pancrelipase (n=24)	Placebo (n=28)
Coefficient of fat absorption		
Baseline, %	54.4±19.5	57.1±20.8
End of double-blind period, %	85.6±6.3	66.3±20.4
Change from baseline, %	32.1±18.5 P<0.0001 vs. placebo[a]	8.8±12.5
Coefficient of nitrogen absorption		
Baseline, %	−78.4±87.1	−89.1±95.0
End of double-blind period, %	13.0±45.4	−64.0±101.5
Change from baseline, %	97.7±82.3 P=0.0013 vs. placebo[a]	24.4±101.0

[a]Treatment comparisons are based on a nonparametric analysis of covariance model including an effect for treatment and with the corresponding baseline as a covariate.

Analysis of efficacy

The change from baseline in CFA was significantly greater with pancrelipase vs. placebo. The mean±s.d. change from baseline CFA values was 32.1±18.5% for pancrelipase and 8.8±12.5% for placebo (P<0.0001; **Table 2**). The outcome of the three supporting analyses carried out on the CFA data was consistent with the primary analysis with significant mean improvements in the pancrelipase group vs. placebo for all three analyses (data not shown).

Sub-analysis of CFA data according to baseline CFA indicated that in patients receiving pancrelipase, the mean±s.d. change from baseline was greater in patients with a baseline CFA ≤50% (more severe EPI) compared with those with a baseline CFA >50%: 55.3±13.6 vs. 22.1±7.3, respectively (significance not tested). However, on-treatment CFA values at the end of the study were similar regardless of baseline CFA: 84.6±9.0 and 87.0±4.2, respectively. Thus, the least squares mean difference in the change from baseline CFA between the pancrelipase and placebo groups was greater in patients with baseline CFA ≤50% (39.7%) compared with those with baseline CFA >50% (13.1%).

On the basis of the dietary information recorded in patient diaries during the stool collection period, the mean±s.d. total fat intake over 72 h was similar in both groups at baseline: pancrelipase 467.3±159.2 g and placebo 444.5±122.3 g. At the end of the treatment phase the mean±s.d. total fat intake was 473.9±177.7 g in the pancrelipase group and 505.4±201.2 g in the placebo group.

A high proportion of patients in both groups had negative CNA values at baseline as indicated by the negative mean CNA values shown in **Table 2**. The mean±s.d. change from baseline in CNA was significantly greater in the pancrelipase group: 97.7±82.3% compared with placebo: 24.4±101.0%; P=0.0013 (**Table 2**). The CNA value remained negative in the placebo group at the end of the double-blind period. Nitrogen intake over 72 h was similar in both groups at baseline with a mean±s.d. of 64.5±31.9 g in the pancrelipase group and 61.1±29.4 g in the placebo group. Nitrogen intake remained consistent in both the groups with mean±s.d.

Table 3. Change from baseline in stool characteristics—full analysis sample

	Pancrelipase (n=24)	Placebo (n=28)	Treatment difference	P value
Stool frequency (per day), LS mean±s.e.	−0.6±0.2	0.2±0.2	−0.8	P=0.005
Stool fat (g), LS mean±s.e.	−147.6±12.7	−34.8±11.5	−112.8	P<0.0001
Stool nitrogen (g), LS mean±s.e.	−54.5±7.9	−8.0±7.1	−46.6	P<0.0001

LS, least squares.

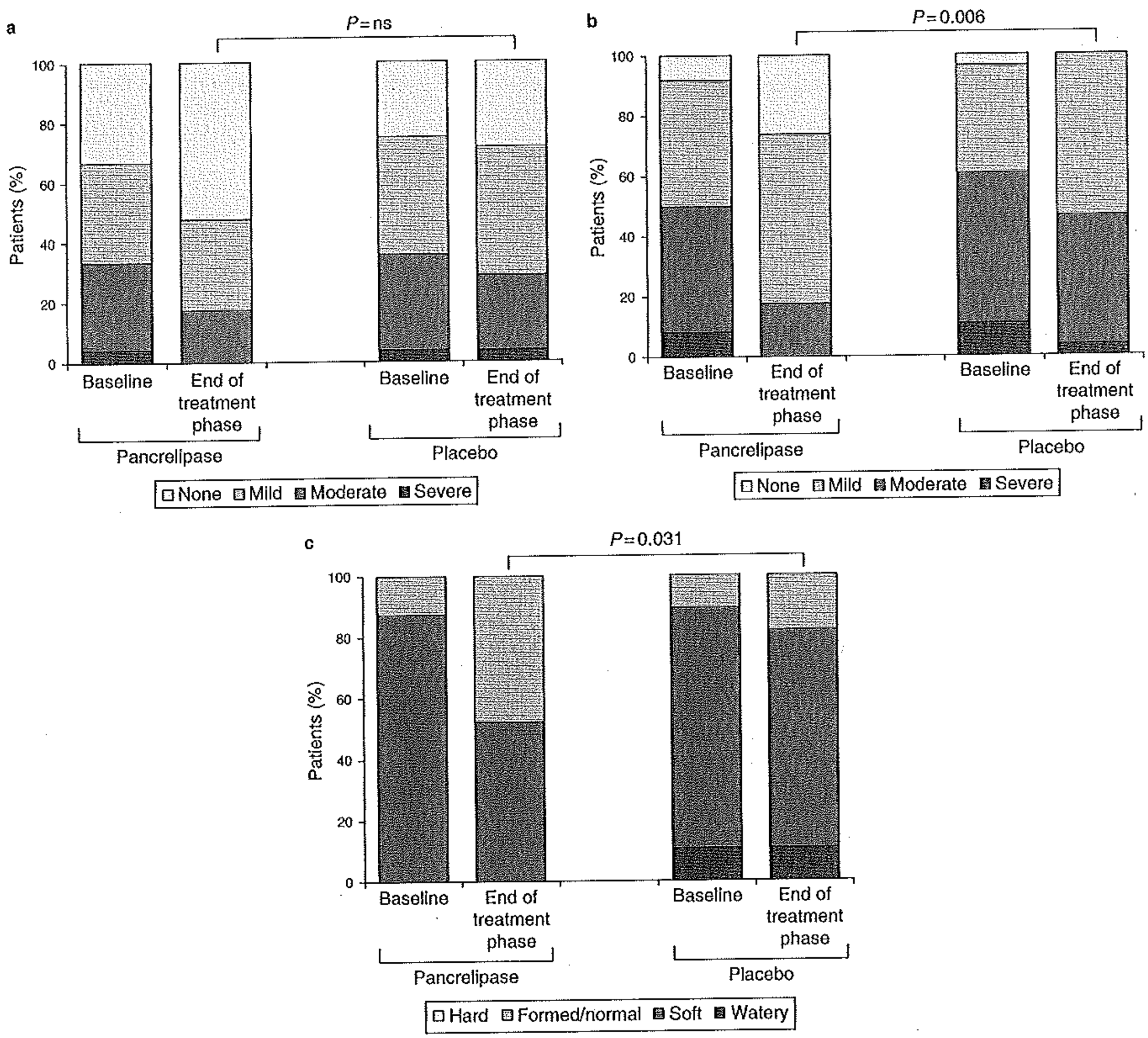

Figure 3. Comparison of clinical symptoms at baseline and at the end of the treatment period for pancrelipase and placebo groups (full analysis sample). (**a**) Abdominal pain, (**b**) flatulence, and (**c**) stool consistency. P values refer to the comparisons between treatment groups at the end of the double-blind treatment phase.

values of 69.3±33.7 g for pancrelipase and 68.1±37.2 g for placebo at the end of the treatment period.

Significant improvements in stool characteristics were observed with pancrelipase compared with placebo, as shown in Table 3. At baseline, clinical symptomatology (abdominal pain, stool consistency, and flatulence) was generally similar in the placebo and pancrelipase groups. There was no meaningful change from baseline to end of treatment in the proportion of patients with none/mild abdominal pain in both groups. There was an increase from baseline to end of treatment in the proportion of patients with formed/normal stools in the pancrelipase group, whereas no substantial change was noted in the placebo group. There was also an increase from baseline to end of treatment in the proportion of patients with no flatulence in the pancrelipase group compared with a decrease in the placebo group. Statistically significant differences were observed between pancrelipase and placebo for flatulence ($P=0.006$) and stool consistency ($P=0.031$) at the end of the treatment period (**Figure 3**).

Safety

The mean duration of exposure to treatment was the same in both groups: 6.8 days in the pancrelipase group and 6.7 days in the placebo group. Few TEAEs were recorded: five (20.0%) patients in the pancrelipase group and six (20.7%) patients in the placebo group reported one or more TEAEs, consisting of mainly GI events and metabolism and nutritional disorders, as listed in **Table 4**. There were no TEAEs with a clinically meaningful greater incidence in the pancrelipase group compared with the placebo group. One patient in each group had TEAEs thought by the investigator to be related to treatment; these included abnormal feces, frequent bowel movements, and inadequate control of diabetes mellitus in the pancrelipase group, and abdominal pain and vomiting in the placebo group. One severe TEAE of abdominal pain was recorded in the placebo group. Non-treatment-emergent serious AEs were observed in two (6.9%) patients in the placebo group (abdominal pain and vitamin B12 deficiency anemia) but resolved before randomization; no serious AEs were reported in the pancrelipase group. No discontinuations owing to AEs or deaths occurred in this study and there were no meaningful treatment group differences observed for any of the laboratory parameters tested or vital signs.

Table 4. Treatment-emergent adverse events occurring in ≥2 patients in any system organ class in either treatment group—safety sample

	Pancrelipase (n=25)	Placebo (n=29)
≥1 Treatment-emergent adverse events, n (%)	5 (20.0)	6 (20.7)
Gastrointestinal disorders, n (%)	2 (8.0)	2 (6.9)
Abnormal feces	1 (4.0)	0
Flatulence	1 (4.0)	0
Abdominal pain	1 (4.0)	1 (3.4)
Abdominal discomfort	0	1 (3.4)
Frequent bowel movements	1 (4.0)	0
Vomiting	0	1 (3.4)
Metabolism and nutrition disorders, n (%)	3 (12.0)	2 (6.9)
Diabetes mellitus inadequate control	1 (4.0)	0
Hyperglycemia	1 (4.0)	2 (6.9)
Hypoglycemia	1 (4.0)	1 (3.4)

DISCUSSION

The need for pancreatic enzyme supplementation in the treatment of maldigestion due to EPI is undisputed; it improves the quality of life and in many cases it is life saving. The data presented here provide evidence that pancrelipase delayed-release 12,000-lipase unit capsules are an effective treatment for maldigestion associated with EPI due to CP and PS at doses of 72,000 lipase units per main meal and 36,000 lipase units per snack. Fat absorption, as measured by the CFA, and nitrogen absorption (a marker for protein absorption), as measured by the CNA, had significantly improved from baseline to the end of the treatment period when pancrelipase was compared with placebo. Overall symptoms of maldigestion also improved from baseline to end of therapy to a greater extent in pancrelipase-treated patients compared with placebo, with significantly greater improvements observed in stool characteristics, flatulence, and stool consistency. Pancrelipase was well tolerated, with a similar AE profile observed to that in the placebo group. A low number of TEAEs was reported overall and those reported were mainly GI events and metabolic/nutritional disorders, which may be attributable to the underlying disease. The good safety profile of pancrelipase provides a particularly favorable benefit to risk ratio.

The CFA is the gold standard surrogate marker of fat absorption. The CFA results in this study are consistent with those of other studies assessing previous formulations of pancrelipase in CP and PS patients. In a double-blind study, patients with CP receiving pancrelipase had a CFA of 86.6% compared with 68.0% on placebo at the end of a 2-week treatment period ($P=0.0185$ for treatment difference) (22). In a further double-blind study enrolling 11 patients who had undergone surgery (local resection–longitudinal pancreaticojejunostomy) for CP, those receiving pancrelipase had a CFA of 83.3% compared with 52.7% in the placebo group at the end of the 4-week randomized treatment period (10). In our study, subanalysis of CFA data by baseline CFA values indicated that there were no differences in CFA values during pancrelipase treatment according to the severity of EPI at baseline; therefore, patients with more severe EPI at baseline had correspondingly larger increases in CFA on pancrelipase.

Use of the CNA to measure protein absorption is currently not well characterized and, to our knowledge, this study represents the first report of CNA measurement in patients with CP. No methodological biases regarding the measurement of protein absorption were identified. The dietary diaries were checked regarding protein/nitrogen intake and were as expected, with no inconsistencies that would explain negative CNA values. In our study, a high proportion of patients had negative CNA values at baseline; in addition the CNA value remained negative in the placebo group at the end of the double-blind period, suggesting a negative protein balance in these patients. Overall, significant improvements from baseline were observed for CNA in the pancrelipase group. Although a small number of patients still had negative CNA values during pancrelipase therapy, there was a clear, significant improvement in nitrogen absorption compared with that in the placebo group at the end of the short treatment time on a high fat diet, with 63.6% of patients on pancrelipase having a positive CNA value at the end of treatment vs. 29.6% on placebo. A potential limitation with respect to interpretation of the nitrogen balance data is that the PERT dose taken before the study-entry may not have been equal to the pancrelipase dose evaluated here. If patients were under-treated before the study, then the tested dose of pancrelipase may have significantly improved digestion of fats, resulting in earlier satiety and lower total consumption. In addition, the diet may have changed from low fat to high fat on study-entry, which, when combined with better digestion of fat, may result in a reduced intake of nitrogen with a temporary, negative nitrogen balance. However, this does not indicate loss of body protein. The extension phase of this study will provide data on the effects of pancrelipase and placebo on serum markers of protein nutrition; it is anticipated that major improvements will be observed as in a previous study by Domínguez-Muñoz *et al.* (18) In a previous double-blind study of patients who had undergone surgery for CP, improvement in CNA (reported as coefficient of protein absorption) with pancrelipase was also reported by Van Hoozen *et al.* (10). Patients received PERT for 4 weeks and were then randomized to a further 4 weeks of pancrelipase or placebo. From week 4 to week 8, the CNA improved from 77% to 84.4% ($P = 0.05$) on pancrelipase compared with a reduction from 82.6% to 70.3% on placebo. Nevertheless, further research is needed to better determine the protein status in patients with CP and PS and the consequences of improving protein absorption in these patients.

In our study, a small change from baseline of 8.8% in the CFA was observed in the placebo group. Although this was statistically significant ($P < 0.05$ vs. baseline), this change is not considered clinically relevant given the inter-subject variation in digestion and the potential for variations in diet even in a controlled environment. An improvement from baseline in CNA in the placebo group of 24.4% was observed (not significant vs. baseline). These small improvements observed in the placebo group are not unexpected; placebo CFA and CNA values within the same range were observed in the two clinical trials of PERT in CP/PS noted above (10,22) and in one trial enrolling patients with CF (23). The large s.d. values observed in the placebo group for CFA and CNA values in the current study indicate a highly variable placebo effect; one possible explanation is adaptation when patients were off-PERT in the placebo run-in period, which is subsequently continued into the randomized period.

In the absence of formalized PERT dosing guidelines in CP, initial dosing is based on the current clinical practice and clinician experience and usually adjusted according to EPI severity, dietary fat content, adequate symptom control, and maintenance of good nutritional status (13,26). Reviews of PERT in CP suggest a variety of dosing ranges, including 20,000 to 75,000 European Pharmacopoeia units of lipase for a main meal (26), approximately 90,000 United States Pharmacopeia (USP) units of lipase per meal to abolish steatorrhea (15), and up to 80,000 units of lipase per meal to achieve desired stool pattern (5). Carrière *et al.* (16) have also suggested that the normal pancreas may not produce lipase much in excess of the amount required for complete dietary fat digestion and therefore much higher PERT doses than currently used may be required to achieve normal fat digestion in patients with severe EPI. It is of note that international units of lipase are not equivalent to other units of lipase measurement such as Federation Internationale du Pharmaceutiques and USP; e.g., 30,000 international units is equivalent to 90,000 USP units (15). A dose of 72,000 lipase units per main meal was selected in this study to ensure that patients with more severe EPI responded to therapy and to take into account the high fat intake from the diet specified in the protocol. This study showed the efficacy and safety (short-term) of pancrelipase at this dose, which is within the ranges recommended in the CP reviews mentioned above. Previous clinical studies of PERT in patients with CP have used lower doses of PERT (10,20,22,33). Use of lower doses in clinical practice may result in many patients with EPI due to CP being undertreated, especially patients who have been receiving low quality generic formulas (15). Although patients with moderate EPI may benefit from lower doses of PERT in terms of improvement in clinical symptoms, indirect functional testing has shown that around two-thirds of patients with EPI due to CP have abnormally low nutritional parameters even when their symptoms are adequately controlled with PERT, emphasizing the need to look beyond symptom control in clinical practice. Sensitive measures of nutritional status should ideally be used in these patients to optimize PERT dose and nutrition (18). As the CFA test does not discriminate between hepatobiliary, mucosal, and pancreatic causes of fat malabsorption, detailed pancreatic imaging and concomitant functional diagnosis in these patients remains essential.

A high number of patients participating in the placebo run-in phase did not enter the double-blind treatment phase of this study because they did not meet the strict interim inclusion criteria requirements defining more severe EPI (CFA <80% and/or stool fat excretion ≥40 g). The initial screening process detected moderate to severe pancreatic insufficiency on the basis of simple tests and provided clinical evidence that the patients were PERT-dependent for the treatment of signs and symptoms of pancreatic disease and maldigestion. The high rate of exclusion after the run-in phase and before randomization suggests that PERT is effective in controlling symptoms of milder EPI than the strict threshold of CFA on placebo that the study protocol required. In addition, there is a significant and highly variable background of GI symptoms and placebo responses that confound some of the subjective symptomatic measurements in this patient population.

The effectiveness of pancrelipase for the most severe degree of EPI (CFA ≤50%) at a dose of 72,000 units of lipase per meal suggests that all degrees of EPI can be successfully treated with PERT. The need for optimizing PERT treatment on the basis of symptomatic and nutritional targets of a wide spectrum of patients in clinical practice was recently shown by Domínguez-Muñoz *et al.* (18) in which

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a PERT with a minimum of 60,000 units of lipase was required in 20% of their patients with CP to improve or normalize body weight, pre-albumin levels, and retinol-binding protein levels. In that study, higher doses of PERT were not tested and patients with no residual pancreatic function (i.e., total pancreatectomy) were not included. Thus, the benefits of pancrelipase observed in the present study are likely to be generalizable to the wider population of patients with EPI due to CP or PS, regardless of EPI severity.

A potential limitation of this study is the slight imbalance in the number of PS patients between treatment groups. The higher proportion of PS patients in the pancrelipase group could provide greater potential for improvement in this group. However, subgroup analysis of CFA by disease status (CP vs. PS) indicated no clinically meaningful differences by disease status in the effect of pancrelipase on the change from baseline CFA (data not shown). In addition, this study provided only a limited time period for safety assessment. There are no safety concerns regarding long-term therapy with pancrelipase delayed-release capsules on the basis of clinical study data and substantial clinical experience. The open-label extension period of this study (to be reported separately) will provide long-term safety data to support the favorable safety profile of pancrelipase delayed-release capsules.

Together, the results of this double-blind, randomized, placebo-controlled study provide strong evidence for the efficacy and safety of pancrelipase delayed-release 12,000-lipase unit capsules in the treatment of EPI due to CP and PS, with significant improvements in fat absorption and protein absorption compared with placebo.

CONFLICT OF INTEREST

Guarantor of the article: David C. Whitcomb, MD, PhD.
Specific author contributions: Study planning and design of protocol: Steven Caras, Suntje Sander-Struckmeier; identified and recruited patients: David C. Whitcomb, Glen A. Lehman, Galina Vasileva, Ewa Malecka-Panas, and Natalya Gubergrits; clinical care of patients: David C. Whitcomb, Glen A. Lehman, Galina Vasileva, Ewa Malecka-Panas, and Natalya Gubergrits; collection of data: David C. Whitcomb, Glen A. Lehman, Galina Vasileva, Ewa Malecka-Panas, and Natalya Gubergrits; analysis of data: Yannan Shen; interpretation of data, contribution towards the development and writing of the paper and approval of the final draft submitted: all authors.
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Potential competing interests: David C. Whitcomb has served as a consultant for Solvay Pharmaceuticals and Axcan Pharma, Birmingham, AL, USA. He owns stock in Ambry Genetics and also the U.S. patent 6406846 entitled "Method for determining whether a human patient is susceptible to hereditary pancreatitis, and primers therefore", which has been licensed and provides royalty income. His research is supported by the National Institutes of Health grants DK061451 and DK054709, the Frieda G. and Saul F. Shapira BRCA Cancer Research Program, and the Wayne Fusaro Pancreatic Cancer Research Fund. Ewa Malecka-Panas is a consultant to Solvay Pharmaceuticals. Yannan Shen and Steven Caras are employees of Solvay Pharmaceuticals Inc. Suntje Sander-Struckmeier is an employee of Solvay Pharmaceuticals GmbH, Hannover, Germany. Glen A. Lehman, Galina Vasileva, and Natalya Gubergrits have no potential competing interests.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

✓ Exocrine pancreatic insufficiency (EPI) is frequent in chronic pancreatitis (CP) and after pancreatic surgery (PS).
✓ Effective management of EPI with pancreatic-enzyme replacement therapy is essential to prevent maldigestion and malnutrition.

WHAT IS NEW HERE

✓ New formulation pancrelipase delayed-release capsules significantly improved fat and nitrogen absorption and clinical symptoms vs. placebo in CP and PS.
✓ This is the first report of coefficient of nitrogen absorption measurement in patients with CP.

REFERENCES

1. Whitcomb DC, Lowe ME. Human pancreatic digestive enzymes. Dig Dis Sci 2007;52:1–17.
2. Falconi M, Mantovani W, Crippa S *et al.* Pancreatic insufficiency after different resections for benign tumours. Br J Surg 2008;95:85–91.
3. Kahl S, Malfertheiner P. Exocrine and endocrine pancreatic insufficiency after pancreatic surgery. Best Pract Res Clin Gastroenterol 2004;18:947–55.
4. Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. Gut 2005;54 (Suppl 6): vi1–28.
5. Abdel Aziz AM, Lehman GA. Current treatment options for chronic pancreatitis. Curr Treat Options Gastroenterol 2007;10:355–68.
6. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 2001;120:682–707.
7. Whitcomb DC, Gorry MC, Preston RA *et al.* Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996;14:141–5.
8. Witt H, Apte MV, Keim V *et al.* Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy. Gastroenterology 2007;132:1557–73.
9. Tanaka M, Chari S, Adsay V *et al.* International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 2006;6:17–32.
10. Van Hoozen CM, Peeke PG, Taubeneck M *et al.* Efficacy of enzyme supplementation after surgery for chronic pancreatitis. Pancreas 1997;14:174–80.
11. Walkowiak J, Sands D, Nowakowska A *et al.* Early decline of pancreatic function in cystic fibrosis patients with class 1 or 2 *CFTR* mutations. J Pediatr Gastroenterol Nutr 2005;40:199–201.
12. Tsiotos GG, Luque-de León E, Sarr MG. Long-term outcome of necrotizing pancreatitis treated by necrosectomy. Br J Surg 1998;85:1650–3.
13. Domínguez-Muñoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. Curr Gastroenterol Rep 2007;9:116–22.
14. DiMagno EP, Go VL, Summerskill WH. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. N Engl J Med 1973;288:813–5.
15. DiMagno MJ, DiMagno EP. Chronic pancreatitis. Curr Opin Gastroenterol 2006;22:487–97.

16. Carrière F, Grandval P, Gregory PC *et al.* Does the pancreas really produce much more lipase than required for fat digestion? JOP 2005;6:206–15.
17. Dumasy V, Delhaye M, Cotton F *et al.* Fat malabsorption screening in chronic pancreatitis. Am J Gastroenterol 2004;99:1350–4.
18. Domínguez-Muñoz JE, Iglesias-García J, Vilariño-Insua M *et al.* [13]C-mixed triglyceride breath test to assess oral enzyme substitution therapy in patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2007;5:484–8.
19. Brady MS, Garson JL, Krug SK *et al.* An enteric-coated high-buffered pancrelipase reduces steatorrhea in patients with cystic fibrosis: a prospective, randomized study. J Am Diet Assoc 2006;106:1181–6.
20. Domínguez-Muñoz JE, Iglesias-García J, Iglesias-Rey M *et al.* Effect of the administration schedule on the therapeutic efficacy of oral pancreatic enzyme supplements in patients with exocrine pancreatic insufficiency: a randomized, three-way crossover study. Aliment Pharmacol Ther 2005;21:993–1000.
21. Konstan MW, Stern RC, Trout JR *et al.* Ultrase MT12 and Ultrase MT20 in the treatment of exocrine pancreatic insufficiency in cystic fibrosis: safety and efficacy. Aliment Pharmacol Ther 2004;20:1365–71.
22. Safdi M, Bekal PK, Martin S *et al.* The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. Pancreas 2006;33:156–62.
23. Stern RC, Eisenberg JD, Wagener JS *et al.* A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. Am J Gastroenterol 2000;95:1932–8.
24. Waljee AK, DiMagno MJ, Wu BU *et al.* Systematic review: pancreatic enzyme treatment of malabsorption associated with chronic pancreatitis. Aliment Pharmacol Ther 2009;29:235–46.
25. Graff GR, McNamara J, Royall J *et al.* Safety and tolerability of a new formulation of pancrelipase delayed-release capsules (CREON®) in children under seven years of age with exocrine pancreatic insufficiency due to cystic fibrosis. an open-label, multicentre, single-treatment-arm study. Clin Drug Investig 2010;30:351–64.
26. Layer P, Keller J, Lankisch PG. Pancreatic enzyme replacement therapy. Curr Gastroenterol Rep 2001;3:101–8.
27. US Food and Drug Administration. FDA requires pancreatic extract manufacturers to submit marketing applications. April 27 2004. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108289.htm. Accessed 26 November 2009.
28. Trapnell BC, Maguiness K, Graff GR *et al.* Efficacy and safety of Creon® 24000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2009;8:370–7.
29. Graff GR, Maguiness K, McNamara J *et al.* Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged 7–11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. Clin Ther 2010;32:89–103.
30. Jeejeebhoy KN, Ahmad S, Kozak G. Determination of fecal fats containing both medium and long chain triglycerides and fatty acids. Clin Biochem 1970;3:157–63.
31. van de Kamer JH, ten Bokkel Huinink H, Weyers HA. Rapid method for the determination of fat in feces. J Biol Chem 1949;177:347–55.
32. Kjeldahl JT. A new method for the determination of nitrogen in organic matter. Z Anal Chem 1883;22:366–82.
33. O'Keefe SJ, Cariem AK, Levy M. The exacerbation of pancreatic endocrine dysfunction by potent pancreatic exocrine supplements in patients with chronic pancreatitis. J Clin Gastroenterol 2001;32:319–23.

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REVIEW

CREON (Pancrelipase Delayed-Release Capsules) for the Treatment of Exocrine Pancreatic Insufficiency

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ABSTRACT

Exocrine pancreatic insufficiency (EPI) is associated with conditions including cystic fibrosis (CF), chronic pancreatitis (CP), and pancreatic surgery (PS). The symptoms include maldigestion, malnutrition, weight loss, flatulence, and steatorrhea. Pancreatic enzyme replacement therapy (PERT) is the standard treatment for EPI; it is regulated in many countries and most recently in the USA following a US FDA mandate for all PERT manufacturers to submit new drug applications. Pancrelipase delayed-release capsules (CREON®, Abbott, Marietta, GA, USA) have been available in Europe since 1984 and in the USA since 1987; a new formulation was the first PERT to gain approval in the USA in 2009. The efficacy and safety of CREON have been demonstrated in double-blind, randomized, placebo-controlled trials in patients with CF aged ≥7 years and in patients with CP or post-PS. The data consistently demonstrate significantly better fat and nitrogen absorption with CREON versus placebo, and improvements in clinical symptoms, stool frequency, and body weight. Additionally, efficacy and safety of CREON have been shown in open-label studies in young children with CF (aged 1 month to 6 years), with control of fat malabsorption and control of clinical symptoms. The most commonly reported adverse events (AEs) with PERT are gastrointestinal disorders and allergic skin reactions. In clinical studies, CREON was well tolerated with very few withdrawals due to AEs and a low frequency of AEs judged treatment related, regardless of patient age. To further support the known safety profile of PERT, all manufacturers are required to investigate risk factors for fibrosing colonopathy, a rare gastrointestinal complication of CF, and the theoretical risk of viral transmission from porcine-derived PERT products. Together, the clinical study data and wealth of clinical

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experience suggest that CREON is effective and safe in patients with EPI regardless of etiology, with a very favorable risk-benefit profile.

Keywords: chronic pancreatitis; CREON®; cystic fibrosis; delayed-release; exocrine pancreatic insufficiency; pancreatin; pancreatic enzyme replacement therapy; pancrelipase

INTRODUCTION

Pancreatic enzyme replacement therapy (PERT) products are prescribed for the treatment of exocrine pancreatic insufficiency (EPI), which is often associated with cystic fibrosis (CF), chronic pancreatitis (CP), malignant ductal obstruction of the pancreas, or pancreatic surgical procedures.[1] The pancreas secretes digestive enzymes (lipase, protease, and amylase) into the duodenal lumen, where they facilitate the breakdown of macronutrients. Thus, patients with untreated EPI typically have difficulty digesting fat and suffer symptoms of both maldigestion and malnutrition, with deficiencies of essential fatty acids and fat-soluble vitamins, weight loss, cramping, flatulence, bloating, and greasy, foul-smelling, loose stools (steatorrhea). The overt clinical symptoms of EPI are mainly a consequence of fat maldigestion. However, protein and carbohydrate maldigestion also contribute to EPI-associated malnutrition, affecting nutritional status and overall health. Protein maldigestion results in excess protein in the stool (creatorrhea) and chronic protein malabsorption may result in hypoalbuminemia, which can lead to generalized edema or ascites. Symptoms of carbohydrate malabsorption include diarrhea, flatulence, and abdominal pain/distension. For patients with CF, inadequate treatment of EPI may have serious consequences for nutritional status, which has been directly correlated with lung function[2,3] and survival.[4,5]

By convention, PERT products are labeled according to the amount of lipase they contain; all PERT products also contain protease and amylase, but the labeled and actual amounts of these two enzymes may differ from product to product even when labeled lipase amounts are the same. Older pancreatic enzyme formulations were based on pancreatin, a substance obtained from the pancreas of the hog or ox. Current PERT formulations are based on pancrelipase, a more potent extract from the hog pancreas, which the US Pharmacopeia (USP)[6] defines as containing not less than 24 USP units of lipase activity, 100 USP units of amylase activity, and 100 USP units of protease activity per mg. International application of these definitions is somewhat confusing, because outside the USA pancrelipase is typically referred to as "pancreatin" even though it is the same active substance with similar potency and activity.

For exogenous PERT to be effective, it is crucial that as much as possible of the dose reaches the proximal small intestine at the same time as the partially digested food (chyme). Lipase is the most sensitive of the pancreatic enzymes to the effects of both pepsin and acid, and is irreversibly inactivated at pH 4.0 or lower.[7] Early PERT preparations consisting of tablets or encapsulated powder were not protected against such inactivation in the stomach, and perhaps only as little as 8% of ingested lipase was bioavailable in the small intestine. Therefore, it was necessary to administer orally up to five to 10 times as much lipase as was required for intraluminal digestion; bicarbonate or H_2 receptor antagonists were often administered concomitantly to attempt to reduce degradation by stomach acid. The development of enteric coatings and microsphere and microtablet formulations in the 1970s made it possible to protect pancreatic enzymes for passage through the stomach, enabling enzyme delivery to the duodenum simultaneously with the chyme, and thus allowing enzyme release when the intestinal pH is most conducive for enzyme activity. This allowed patients with CF to shift from the previously recommended low-fat, high-protein program to a diet high in fat as well as protein, making it possible for them to meet their high energy needs. Subsequent refinements in microencapsulation technology have facilitated increases in lipase content and more efficient dosing.[8,9]

Previous studies have suggested that PERT products vary in terms of actual enzyme content and in-vitro response to simulated gastric and duodenal conditions.[10-12] As pancreatic enzymes are sensitive proteins and liable to inactivation, capsules were routinely overfilled to ensure that potency would not drop below label claims before the end of shelf-life.[13] Over the past decade, the USP standard has evolved in recognition of these circumstances and actually states upper and lower limits of labeled amounts of enzymes. Currently, the US Food and Drug Administration (FDA) labeling requirements mandate that approved pancreatic enzymes in the USA have no stability overfill and hence new preparations are labeled accordingly.

PERT products are approved around the world; however, because PERT products were available before the passage of the 1938 Federal Food, Drug, and Cosmetic Act, they have historically been, in the absence of any specific concerns, marketed in the USA without any requirements for safety and efficacy testing. These prescribed products have been documented with in-vitro performance studies and in-vivo clinical efficacy data.[12-18] Citing concerns about the significant differences in bioavailability among PERT products and consequent instances of serious under- and over-dosing, the FDA formally announced in 2004 the New Drug Application requirement for EPI drug products,[19] with the stipulation that because the drugs are "medically necessary," manufacturers could continue to market their products without an approved application for the next 4 years, which was extended until May 2010. To date, three pancreatic enzyme preparations are on the market in the USA that have received FDA approval: CREON® (pancrelipase delayed-release capsules; Abbott, Marietta, GA, USA) in April 2009, Zenpep® ([pancrelipase] Delayed Release Capsules; Eurand Pharmaceuticals Ltd, Yardley, PA, USA) in August 2009, and Pancreaze™ ([pancrelipase] delayed-release capsules; McNeil Pharmaceuticals, Ruritan, NJ, USA) in April 2010. These products represent the first enteric-coated pancrelipase preparations approved in the USA since the introduction of crude extracts over 50 years ago to treat infants with CF, and all are of porcine origin. As new dosage forms are approved, some manufacturers have taken the opportunity to modify their formulations with regards to excipients, improved packaging, and stability to allow for a more consistent delivery of pancreatic enzymes.

CREON INDICATIONS AND PRESCRIBING INFORMATION

CREON is indicated for the treatment of EPI due to CF, CP, pancreatectomy, and other conditions in which EPI is present.[20] Dosages are individually titrated based on clinical symptoms and the degree of steatorrhea, and are adjusted for the amount of dietary fat consumed. For patients with CF, guidelines from the CF Consensus Conferences[21-24] are used for initiating PERT and are summarized in Table 1. Dosing in patients with CF and CP will also be discussed in later sections. CREON capsules should be swallowed whole and not crushed or chewed. Capsules can be opened and the contents given on a spoon mixed with soft acidic food, such as applesauce, until children are able to swallow

Table 1. Cystic Fibrosis Consensus Conference dosing guidelines for pancreatic enzyme replacement therapy.[21-25]

Infants up to 12 months	2000-4000 IU lipase/120 mL of formula or per breast feeding
Children 12 months to 4 years	1000 IU lipase/kg body weight/meal to a maximum of 2500 IU/kg body weight/meal (daily maximum of 10,000 IU/kg/day or 4000 IU/g dietary fat/day)
Children 4 years and older and adults	500 IU lipase/kg body weight/meal to a maximum of 2500 IU/kg body weight/meal (daily maximum of 10,000 IU/kg/day or 4000 IU/g dietary fat/day)

IU=international unit.

capsules whole; this mixture should be given during meals, immediately after mixing.[20] If capsules are opened, care should be taken to mix the contents only with foods of pH ≤4.5 to avoid disruption of the protective enteric coating and thus early release of enzymes and/or loss of enzyme activity before ingestion.[20] As CREON is an enteric-coated formulation and therefore protected against gastric acid inactivation, routine administration of a concomitant proton pump inhibitor or H_2 receptor antagonist is not required.

The active pharmaceutical ingredient of CREON is pancrelipase, a porcine pancreatic extract containing multiple enzyme classes. Each delayed-release gelatin capsule for oral administration contains enteric-coated spheres approximately 1 mm in diameter.[20] The following inactive ingredients are also present in the current FDA-approved formulation: cetyl alcohol, dimethicone, hypromellose phthalate, polyethylene glycol, and triethyl citrate.[20] The inactive ingredients differ from previous formulations in that light mineral oil has been removed from the spheres and dibutyl phthalate has been removed from the enteric coating in response to general FDA and European Union directives, respectively.

By convention, PERT preparations listed with a numerical value refer to the thousands of units of lipase per dosage form contained in the product. In the USA, USP standards are used for pancrelipase, while in Europe other standards are used including European Pharmacopoeia (Ph. Eur.)/Fédération Internationale Pharmaceutique (FIP) units. Standardization of lipase units has occurred (1 USP=1 Ph. Eur.=1 FIP unit) but there are differences with regards to amylase and protease unit standards. As PERT is traditionally dosed based on lipase units, we can use them interchangeably and no conversion is needed.[26,27]

Enteric-coated (delayed-release) CREON formulations have been available in Europe since 1984 and in the USA since 1987. Currently, in the USA, CREON is available in three strengths, containing 6000, 12,000, and 24,000 USP units of lipase per capsule.[20] In addition, protease and amylase are included in these preparations in the amounts shown in Table 2.

Other formulations of CREON (with the same active ingredient) are available outside the US (Creon 10000 Ph. Eur., Creon 25000 Ph. Eur., Creon 40000 Ph. Eur. and a special formulation

Table 2. CREON dosage forms and strengths currently available in the USA.[20]

	USP units		
	Lipase	Protease	Amylase
CREON 6,000	6000	19,000	30,000
CREON 12,000	12,000	38,000	60,000
CREON 24,000	24,000	76,000	120,000

USP=United States Pharmacopeia.

The 6000, 12,000, and 24,000 strengths are equivalent in lipase activity to previously available Creon 5, 10, and 20, respectively.

for children, Creon micro [5000 Ph. Eur. lipase units per dosing scoop]).

CYSTIC FIBROSIS

Overview of Exocrine Pancreatic Insufficiency in Cystic Fibrosis and Long-term Consequences

EPI is present in approximately 85% of patients with CF overall and in up to 99% of patients who are F508del homozygotes, most often from birth.[28-30] The clinical triad of increased appetite, steatorrhea, and malnutrition is highly suggestive of CF with EPI. Nowadays, with increasing worldwide implementation of newborn screening programs,[31] CF is usually diagnosed in very early life. Nevertheless, at initial consultation, half of all infants with CF are symptomatic for EPI and the majority present with impaired growth, low body weight, and digestive symptoms.[32] In addition to malnutrition and steatorrhea, other frequent symptoms include abdominal pain, bloating, flatulence, and rectal prolapse.[27,33] EPI can also lead to edema caused by hypoalbuminemia, deficiencies in fat-soluble vitamins, and hemolytic anemia related to vitamin E deficiency. Even in the context of symptoms, a laboratory test to define pancreatic function status or confirm fat excretion levels is recommended.[21,27] The fecal elastase-1 test is highly sensitive (using a monoclonal rather than polyclonal antibody) and involves an enzyme-linked immunosorbent assay to determine levels of this human pancreas-specific enzyme in a small specimen of well-formed feces; thus it is simply a diagnostic tool of pancreatic function.[34,35] Assessment of the coefficient of fat absorption (CFA) involves 72-hour stool collection, recording of dietary fat during the stool collection period, and calculation of the percentage CFA.[36,37] This test, which is very cumbersome for the patient, is the most valuable tool for assessing fat maldigestion in PERT-supplemented patients with poor nutritional status or inadequately controlled gastrointestinal symptoms, or in clinical trials to evaluate PERT efficacy.

It has been documented that newborn screening programs for CF confer nutritional advantages, as a result of earlier diagnosis, compared with traditional CF diagnosis based on clinical symptoms.[38] As better nutritional status and growth is strongly associated with improved pulmonary function and improved survival in CF,[2-4,39] prompt nutritional support and PERT should be provided as soon as EPI is confirmed, whatever the patient's age and mode of feeding, in order to maintain normal growth status.

Current Recommendations and Practice for the Treatment of Exocrine Pancreatic Insufficiency in Cystic Fibrosis

The standard of care for EPI is based on oral PERT, regardless of etiology. The dosing guidelines for patients with CF are summarized in Table 1.[21-25] The occurrence in the 1990s of fibrosing colonopathy (FC) in young children receiving very high daily doses of PERT[40,41] had a major impact on PERT prescriptions, despite the rarity of this severe gastrointestinal complication. As a result, consensus guidelines for PERT published in 1995 and 2002 recommended that daily doses should not exceed the equivalent of 10,000 IU lipase/kg/day or 4000 IU lipase/g dietary fat/day.[21-23] However, it should be noted that these dosing recommendations were based on older PERT formulations, which were overfilled in terms of lipase units.[11-13,18] Therefore, some patients may have been receiving actual doses that exceeded the recommended upper limit. In the current era of better controlled manufacturing processes, and the US FDA

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requirements for PERT labeling to state actual lipase content, these dosing recommendations and limits may need to be revisited.

Studies have shown that standard- and high-strength PERT preparations provide similar efficacy in terms of fat absorption, as summarized by Littlewood et al.;[27] standard-strength enzyme preparations are recommended for infants and children. Many factors may affect enzyme efficacy; dose requirements therefore remain approximate and doses should be individualized. Adequate PERT should enable the patient to eat a normal or high-fat diet without unpleasant gastrointestinal symptoms and to achieve a satisfactory nutritional and growth status.[27] PERT should be given with all fat- and protein-containing foods, according to the dosing guidelines, with pancreatic enzyme dosage gradually increased on a dietician's or physician's advice if needed until symptom relief and adequate weight gain are achieved. Individualization of doses is supported by a recent report of evidence-based practice recommendations from the Cystic Fibrosis Foundation (CFF) Growth and Nutrition Subcommittee,[25] which concluded that there was insufficient evidence for making recommendations regarding specific PERT doses and CFA values or growth status; there was also insufficient evidence to support the efficacy of generic PERT formulations.

Efficacy of CREON in Cystic Fibrosis

The efficacy of the various formulations of CREON (with the same active ingredient) has been confirmed through extensive clinical experience and in a number of clinical studies in patients with CF.[17,42-47] A summary of published efficacy data from six clinical studies investigating formulations that are currently available in either the USA or Europe is provided in Table 3. A seventh study reporting use of a pre-FDA mandate US formulation (Creon 20[17]) has also been included as this formulation has equivalent lipase content per capsule to current CREON 24,000 USP, with similar pharmaceutical characteristics and sphere size, and therefore provides valid efficacy and safety information. Four studies had an open-label design without placebo control as they included infants and young children.[44-47] The target lipase doses in these studies were selected according to the CFF and EU consensus guidelines[21-24] relevant to the age group under investigation. The three recent studies carried out in the USA used the new formulation of CREON that is now currently available.[42-44]

The data summarized in Table 3 provide substantial evidence for the efficacy of the different CREON formulations in significantly improving fat absorption (as measured by the CFA) versus placebo or baseline (no treatment). On-treatment efficacy appears to be consistent regardless of study design, patient age, and CREON formulation, with CREON demonstrating efficacy in improving malabsorption in preschool-age children[44-46] as well as older children and adults. Improvements were also seen with CREON in secondary outcome measures such as the coefficient of nitrogen absorption (CNA), clinical symptoms, stool frequency, and body weight (Table 3). The CNA is measured in the same way as the CFA but with assessment of nitrogen as a marker for protein absorption. Comparison of data from two randomized, double-blind, placebo-controlled studies with the FDA-approved formulation of CREON indicates consistent on-treatment efficacy in patients aged 7-11 years and patients aged ≥12 years: mean CFA 82.8% and 88.6% and mean CNA 80.3% and 85.1%, respectively.[42,43] Significant improvements in these parameters versus placebo were seen with CREON in both

Table 3. Summary of CREON efficacy in clinical studies enrolling patients with exocrine pancreatic insufficiency due to cystic fibrosis.

Study	*n*	Age group	Study design	Treatment	Mean CFA on CREON	Mean CFA on placebo/ at baseline	*P*-value	Other relevant outcomes
Formulations currently available in the USA (FDA-approved)								
Trapnell et al., 2009[42]	32	≥12 years	Multicenter, double-blind, randomized, placebo-controlled, crossover	CREON 24,000 or placebo for 5 days each	88.6%*	49.6%*	<0.001	Mean* CNA 85.1% on CREON vs. 49.9% placebo (*P*<0.001) Mean* daily stool frequency 1.8 on CREON vs. 2.8 placebo (*P*<0.001) Abdominal pain and flatulence less severe and stool consistency less watery on CREON vs. placebo
Graff et al., 2010[43]	17	7-11 years	Multicenter, randomized, double-blind, placebo-controlled, crossover	CREON 12,000 or placebo for 5 days each	82.8%*	47.4%*	<0.001	Mean* CNA 80.3% on CREON vs. 45.0% placebo (*P*<0.001) Stool frequency/day 1.9 on CREON vs. 3.4 placebo (*P*<0.001) Abdominal pain, flatulence, and stool consistency better on CREON
Graff et al., 2010[44]	18	<7 years	Multicenter, open-label, single arm	CREON 3,000, 6,000, and 12,000 for 10-14 days after standard therapy	Spot stool fat 28.1%	Spot stool fat 27.9%†	NT	Abdominal pain, stool consistency, and flatulence similar for CREON and standard therapy Slightly more day-to-day variability in mean daily stool frequency on standard therapy vs. CREON
Formulations currently available in Europe								
Colombo et al., 2009[45]	12	1-24 months	Multicenter, open-label, single arm	Creon for Children (Creon micro‡) for 8 weeks (CFA measured after 2 weeks)	84.7%	58.0%§	0.0013§	Patients with steatorrhea decreased from 100% to 58% over 2 weeks Mean weight change +1.0 kg over 8 weeks Mean stool frequency change −0.7/day Days with normal stool +11% Days with no gastrointestinal symptoms +13%

(continued on next page)

Table 3. Summary of CREON efficacy in clinical studies enrolling patients with exocrine pancreatic insufficiency due to cystic fibrosis. *(Continued)*

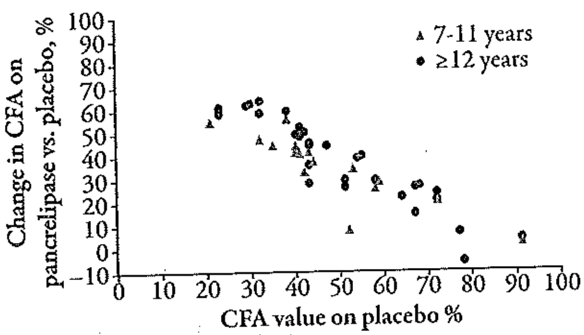
Study	*n*	Age group	Study design	Treatment	Mean CFA on CREON	Mean CFA on placebo/ at baseline	*P*-value	Other relevant outcomes
Formulations currently available in Europe *(Continued)*								
Munck et al., 2009[46]	40	6-36 months	Multicenter, open-label, randomized, crossover	Creon for Children (Creon micro‡) and Creon 10000 for 2 weeks each	77.8%¶ 78.7%¶	NA	NA	Stools formed/normal on 47.8% and 42.6% days¶ Free from abdominal pain on 91% days (both groups) Mild flatulence on 23.1% and 34.9% of days¶
Patchell et al., 2002[47]	59	3-17 years	Multicenter, randomized, open-label, crossover	Creon 10000 MMS for 28 days**	91.3%	NA	NA	Median stool frequency 2/day Majority of stools formed in consistency Flatulence and abdominal pain mainly absent or mild
Other formulations								
Stern et al., 2000[17]	47	7-18 years	Multicenter, randomized, double-blind, placebo-controlled	Creon 20 or placebo for 5-7 days after open-label run-in on CREON	84.1%	52.2%	<0.001	Stool frequency 8/72 h on CREON vs. 12/72 h placebo Formed stools 83% patients on CREON vs. 5% placebo
	50	18-40 years			87.2%	50.9%	<0.001	Stool frequency 7/72 h on CREON vs. 14/72 h placebo Formed stools 67% patients on CREON vs. 22% placebo

CFA=coefficient of fat absorption; CNA=coefficient of nitrogen absorption; FDA=US Food and Drug Administration; MMS=minimicrospheres; NA=not applicable; NT=not tested.
*Least squares mean reported.
†Value on standard therapy before CREON treatment phase.
‡5000 Ph. Eur. lipase units per dosing spoon.
§Baseline-controlled study (without treatment).
¶Values for Creon for Children (Creon micro) and CREON 10000, respectively.
**Reference control was Creon 8000 MS (formulation no longer available).

trials and improvements in clinical symptoms were also consistent (Table 3). The outcomes in the CREON clinical trials compare favorably with normal CFA and CNA values; a study of 16 healthy individuals indicated a mean CFA value of 94% and a mean CNA value of 88%.[48]

Combining individual patient data for on-treatment CFA values and changes in CFA versus placebo from the two randomized, double-blind, placebo-controlled studies with the FDA-approved formulation of CREON[42,43] indicated no apparent differences in CFA values on-treatment according to the severity of EPI (as measured by the CFA during placebo treatment). Thus, patients with more severe EPI (lower CFA on placebo) had correspondingly larger increases in their CFA on CREON treatment, and all subjects with a placebo CFA of less than 40% had an on-treatment difference from placebo of over 30% (Figure 1). No obvious differences were observed regarding efficacy of CREON for the different age groups (Figure 1). In the Trapnell et al.[42] study, prospectively planned subanalyses showed no differences in terms of CFA, CNA, abdominal pain, stool consistency, and flatulence between subjects aged 12-18 years and those aged >18 years.

Figure 1. On-treatment coefficient of fat absorption (CFA) in the two double-blind, placebo-controlled studies with the US Food and Drug Administration-approved formulation of CREON in patients with cystic fibrosis: difference between on-treatment and placebo CFA as a function of placebo CFA (lower placebo CFA indicates more severe exocrine pancreatic insufficiency).



Safety of CREON in Cystic Fibrosis

The long-term safety profile of PERT, such as CREON, has been described in the medical literature, with the most commonly reported adverse events being gastrointestinal disorders and allergic skin reactions (rash, urticaria).[20] Table 4 summarizes treatment-emergent adverse events (TEAEs) occurring in six published clinical studies of CREON that report safety data on currently available formulations.[17,42-46]

TEAEs were generally more frequent with placebo compared with CREON, reflecting the effects of untreated EPI in these patients. The majority of patients completed treatment in these studies, and there were very few withdrawals due to TEAEs, indicating that CREON was well tolerated. As expected due to the nature of the underlying disease, gastrointestinal disorders were the most frequent class of TEAEs on both CREON and placebo. There was a low frequency of TEAEs judged to be probably or possibly treatment related in patients receiving CREON. Serious TEAEs were a severe *Pseudomonas* species lung infection and bronchial obstruction in the study by Munck et al.[46] and hospitalization for pulmonary exacerbation in the study by Stern et al.[17]

There were no obvious trends for TEAEs in patients with CF by age group. Safety data from studies with the new FDA-approved formulation[42-44] are consistent with those of other formulations, with low frequencies of treatment-related TEAEs and withdrawals due to TEAEs. Global post-marketing surveillance data on the various CREON formulations have been collected since January 1984; no data have been noted during this time that would suggest any safety issues associated with CREON formulations.[49]

Taken together, these data indicate that CREON is safe and well tolerated in patients with

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Table 4. Summary of CREON safety in clinical studies enrolling patients with exocrine pancreatic insufficiency due to cystic fibrosis.

Study	*n*	Age group	Most common TEAE class (>20% any group)	Overall TEAEs, *n* (%)		Treatment-related TEAEs, *n* (%)		Withdrawals due to TEAEs, *n* (%)		Serious TEAEs, *n* (%)	
				CREON	PBO	CREON	PBO	CREON	PBO	CREON	PBO
Formulations currently available in the USA (FDA-approved)											
Trapnell et al., 2009[42]	32	≥12 years	GI disorders, nervous system disorders	14 (43.8)	20 (64.5)	6 (18.8)*	12 (38.7)*	1 (3.1)	0	0	0
Graff et al., 2010[43]	17	7-11 years	GI disorders	5 (29.4)	9 (56.3)	0	4 (25.0) [diarrhea, flatulence, abdominal pain, frequent bowel movements, weight decrease, rash]	0	0	0	0
Graff et al., 2010[44]	18	<7 years	Infections and infestations	9 (50.0)	NA	1 (5.6) [diaper rash]	NA	0	NA	0	NA
Formulations currently available in Europe											
Colombo et al., 2009[45]	12	1-24 months	Fever, cough	9 (75.0)	NA	2 (16.7) [constipation]	NA	0	NA	0	NA
Munck et al., 2009[46]	40	6-36 months	URTI, GI disorders§	CfC 17 (42.5)	NA	3 (7.5) [abdominal pain, constipation, vomiting]	NA	1 (2.5)	NA	1 (2.5)	NA
				Creon 10000 17 (42.5)	NA	1 (2.5) [severe dermatitis diaper]	NA	0	NA	1 (2.5)	NA
Other formulations											
Stern et al., 2000[17]	47	7-18 years	Body as a whole, GI disorders, respiratory†	11 (61.1)†	14 (70.0)†	NR	NR	0	1 (5.0)	0	0
	50	18-40 years	Body as a whole, GI disorders†	7 (38.9)†	12 (66.7)†	NR	NR	2 (11.1)‡	1 (5.6)	1 (5.6)‡	0

CfC=Creon for Children (Creon micro); FDA=US Food and Drug Administration; GI=gastrointestinal; NA=not applicable; NR=not reported; PBO=placebo; TEAE=treatment-emergent adverse event; URTI=upper respiratory tract infections.
*Individual events not reported.
†Occurring during double-blind phase only.
‡Occurred during open-label run-in phase.
§Frequency not reported.

EPI due to CF irrespective of age, highlighting its favorable risk–benefit profile in these patients.

CHRONIC PANCREATITIS AND OTHER PATIENT POPULATIONS

Overview of Exocrine Pancreatic Insufficiency in Chronic Pancreatitis and Long-term Consequences

CP is the most common cause of EPI in adults and the most common underlying etiology is alcohol abuse. In 1788, Cawley reported on a "free living young man" who had died of emaciation and diabetes whose post mortem examination revealed multiple pancreatic calculi.[50] Since that early description thousands of reports have been published. We now know that this multifactorial condition is characterized by chronic inflammation with subsequent loss of exocrine and occasionally endocrine parenchyma, with fibrotic tissue replacement, ultimately resulting in maldigestion, malnutrition, and diabetes mellitus. The exact mechanisms triggering and perpetuating the disease are not fully understood, but there is a complex interaction between noxious stimuli, the environment, and genetic predisposition that leads to an excessive inflammatory response with subsequent tissue destruction. However, our understanding of this condition has increased over the past few years and molecular and cellular events contributing to chronic inflammation with subsequent tissue destruction are better understood, particularly the important role that genes and the environment (alcohol consumption and cigarette smoking being independent risk factors) play in this complex condition.[51,52] Other etiologies that lead to EPI include tumors that obstruct pancreatic enzyme secretion (pancreatic cancer, intraductal papillary mucinous neoplasia, ampullary tumors), genetic mutations (CF, cationic trypsinogen, chymotrypsin C, and serine protease inhibitor Kazal type 1), extensive necrotizing pancreatitis, and different types of pancreatic surgery (PS), such as local resection, longitudinal pancreaticojejunostomy, and total pancreatectomy, with EPI severity depending on the type and extent of surgery.[53,54]

Patients with CP usually present with chronic recurrent abdominal pain and then, over a period of many years, CP may lead to steatorrhea (defined as >7 g of fecal fat/day while consuming a 100 g fat diet, with clinical/symptomatic steatorrhea seen when >15 g/day[55]), malnutrition, and occasionally endocrine pancreatic dysfunction, but this may vary based on the etiology of CP. Steatorrhea occurs in CP only after the pancreatic enzyme output has diminished by 90% of normal levels.[56,57] The large reserve capacity of the pancreas noted in earlier studies may be due to the non-pancreatic gastric and lingual lipases.[58]

The diagnosis of CP can be made on the basis of clinical symptoms in combination with structural and functional criteria, but in some patients it can be very difficult to make. Structural changes may take years to develop and functional tests can be normal or not easily accessible; chronic abdominal pain may or may not be present. It is important to recognize and treat EPI in patients with CP to prevent maldigestion of fat, proteins, and carbohydrates, malnutrition, and weight loss. In healthy individuals, fat-soluble vitamins are absorbed from the small intestine along with digested dietary fats via micelles (aggregates of monoglycerides, fatty acids, and bile salts). Deficiencies in fat-soluble vitamins A, E, and K are therefore often present in patients with EPI as a result of fat maldigestion (and therefore reduced micelle formation), and may lead to symptoms such as impaired night-time vision, cerebellar ataxia, and/or increased prothrombin time,[59-61] and vitamin B_{12} deficiency may be present due to both impaired release of the B_{12} complex and bacterial overgrowth in the intestine.[62] Compared with healthy controls, patients with CP have lower serum levels of vitamin D and decreased bone mineral density.[63-65]

Summary of Current Practice for Pancreatic Enzyme Replacement Therapy for the Treatment of Exocrine Pancreatic Insufficiency in Chronic Pancreatitis

As previously mentioned, the standard of care for EPI regardless of underlying etiology is oral PERT. There are currently few formal dosing guidelines for PERT in CP. Approximately 90,000 USP or Ph. Eur. units of lipase must reach the duodenum at the same time as ingested food to assure maximal fat digestion and absorption in patients with EPI. As some endogenous lipase secretion is usually preserved in CP, a starting dose of PERT of 25,000-40,000 USP/Ph. Eur. units of lipase per meal is recommended for the vast majority of patients,[26,66,67] which can then be adjusted based on individual clinical need (symptom severity, degree of steatorrhea, and fat content of diet). To date, there are no studies showing that PERT corrects fat-soluble vitamin deficiencies or B_{12} deficiency without simultaneous vitamin supplementation.[59,62]

Efficacy and Safety of CREON in Chronic Pancreatitis and Other Populations

Randomized and/or placebo-controlled trials of CREON in patients with EPI due to CP or PS have shown improvement of steatorrhea, as measured by increased fat absorption, reduced fecal fat excretion, decreased stool weight and frequency, improved stool consistency, and improved symptom scores.[54,67-71] Another prospective study has shown improvement in quality of life.[72]

In a recent randomized, double-blind, placebo-controlled study by Whitcomb et al.,[71] a new formulation of CREON 12,000 lipase unit (USP) capsules was shown to be safe and effective when patients with CP or post-PS were treated with 72,000 lipase units (USP) per main meal and 36,000 lipase units (USP) per snack compared with placebo for 7 days following a 5-day placebo run-in period (n=54). The change from baseline in CFA was significantly greater with CREON compared with placebo: mean±standard deviation 32.1%±18.5% versus 8.8%±12.5% (P<0.0001). Greater improvements from baseline in stool frequency, stool consistency, abdominal pain, and flatulence were also observed with CREON over placebo. TEAEs were reported in five patients (20.0%) in the CREON group and in six (20.7%) in the placebo group, the most common being gastrointestinal events and metabolism/nutrition disorders. There were no treatment discontinuations due to TEAEs in this study.

A prospective, crossover, randomized, controlled trial by Domínguez-Muñoz et al.[67] in 24 patients with CP and EPI evaluated the effect of the administration schedules of CREON (the Creon 10000 formulation currently available in Europe). The dosing schedules were four capsules before meals (schedule A), four capsules after meals (schedule B), or four capsules throughout the meal (one before, two during, and one after; schedule C). Regardless of the administration schedule used, CREON improved fat digestion in all patients, with recovery rates of 54% with schedule A, 61% with schedule B, and 61% with schedule C (all P<0.0001 versus baseline value of 24%) using the ^{13}C-mixed triglyceride breath test. There was no difference in patients' preference for the three dosing schedules in this study. Fat digestion was optimal when the enzyme preparations were taken during or after meals, and tended to be better than that observed when capsules were administered just before meals although the differences were not significant; therefore, these results should not be used as a recommendation for CREON dosing. The US prescribing information for CREON recommends administration during meals in all patients with EPI;[20] however, in practice, PERT is often administered before meals as well as during meals in patients with CF, whereas in non-CF patients it is often administered after meals.

In a randomized, double-blind, multicenter, placebo-controlled trial, 27 patients with CP received four capsules of CREON (Creon 10; a pre-FDA mandate formulation with equivalent lipase content per capsule to current CREON 12,000 USP) with each meal (two capsules with snacks) for 2 weeks, following a 2-week placebo run-in period.[70] Patients receiving CREON for 2 weeks had a significantly higher mean change in CFA compared with those receiving placebo: +36.7% versus +12.1% (P=0.0185). Compared with placebo, CREON also decreased stool frequency (5.2 per day vs. 14.6 per day; P=0.0015), controlled steatorrhea (change in stool fat excretion –56.6 g/day vs. –11.4 g/day; P=0.0181), and improved stool consistency (stools became more firm in seven subjects vs. one subject; P=0.0102 for overall consistency). No major adverse effects were reported in this small study.

The efficacy of CREON in maintaining postoperative digestion and nutrition in 11 patients who underwent local resection-longitudinal pancreaticojejunostomy for CP was evaluated in a placebo-controlled trial (using Creon 8000, a previous formulation no longer available) at different doses based on initial daily fat excretion.[54] Patients who received CREON showed significant improvements in the CFA (83.3% vs. 52.7%; P=0.02) and the coefficient of total energy absorption (88.3% vs. 71.9%; P=0.02) when compared with placebo. Of interest, the nutritional status of these patients was not significantly altered over the period of the study, although four of five patients receiving CREON gained more than 3.6 kg body weight whereas none of the six patients receiving placebo gained weight. These data suggest that postoperative PERT is necessary and effective in improving absorption in patients with CP after local resection-longitudinal pancreaticojejunostomy.

PANCREATIC ENZYME REPLACEMENT THERAPY TREATMENT FAILURES

In clinical practice, some patients do not respond adequately to PERT and they should be encouraged to discuss openly with their healthcare team any problems they have. In these cases, various other factors may be involved, such as lack of patient compliance, suboptimal PERT dosing, miscalculation of fat intake, deficiency of pancreatic bicarbonate secretion, abnormal composition of bile salts, intestinal ion transport abnormalities, intestinal inflammation, altered gut motility, bacterial overgrowth, and impaired absorption of long chain fatty acids.[26,66,73] High-fiber diets have been associated with a small but significant increase in fecal fat excretion in patients with CP with EPI.[74] In addition, calcium- and magnesium-containing antacids are associated with the formation of soaps and the precipitation of glycine-conjugated bile salts in the intestine, which may lead to worsening of steatorrhea in patients with underlying EPI.[75] Factors related to the PERT preparation itself may have an impact, including the size of the enzyme particles, the dissolution characteristics of the preparation, the rate of emptying from the stomach, and the timing of intake in relation to meals. Variations in the enzyme content of PERT preparations was a potential consideration in the USA before the introduction of the newly approved PERT preparations, as noted earlier in this review. With the new preparations, this is not expected to be an issue.

In compliant patients who do not respond to PERT, increasing the dose twofold and decreasing the amount of fat in meals may be an option in non-CF patients with EPI. Patients with EPI commonly have lower pancreatic bicarbonate secretion, which may become insufficient, resulting in a pH level in the duodenum and small intestine that is too low for adequate dissolution of the PERT enteric coating.[21,66,73] While bicarbonate transport is difficult to treat, intestinal pH can be raised to optimize PERT dissolution by increasing the pH of gastric secretions flowing into the duodenum. Furthermore, increasing duodenal pH may reduce the precipitation of bile salts. Thus, if symptoms of maldigestion persist, adding an H_2 receptor antagonist or a proton pump inhibitor may be beneficial in improving PERT efficacy,[76-78] as is currently prescribed in patients with CF. If all of the above fail, other digestive conditions that may interfere with intestinal absorption should be considered, such as bacterial overgrowth, giardiasis, celiac disease, or blind loop syndrome after gut surgery.[26,66] A complete medical assessment is needed in the absence of clinical improvement.

POTENTIAL RISKS OF PANCREATIC ENZYME REPLACEMENT THERAPY

Fibrosing Colonopathy

FC is a painful condition characterized by shortening and fibrosis of the colon,[79] and is a recognized gastrointestinal complication seen almost exclusively in patients with CF. Littlewood[80] characterized this condition as:

- "Severe submucosal thickening by mature fibrous connective tissue
- Intraluminal fusiform narrowing but with little change in the external bowel diameter, mainly in distal caecum and ascending colon
- Loss of haustral pattern sometimes with a 'cobblestone' appearance of the intestinal epithelium, although the epithelium is generally intact but with some localized defects. Altered architecture suggests there has been repair of previous damage
- Little or no evidence of inflammation or other lesions suggesting Crohn's disease. Some slight inflammation and fat around blood vessels
- The small bowel is not involved
- A few patients have chylous ascites."

FC symptoms include abdominal pain, diarrhea, hematochezia (bloody stools), and, in some cases, partial or complete abdominal obstruction where significant narrowing or stricture has occurred. Treatment of FC ranges from reduction in excessive doses of pancreatic enzymes to surgery (eg, partial or total colonic resection).

The first reported case of FC in the USA occurred in 1991[81] and five cases occurring in Europe had been reported by 1993.[82] The only apparent common factor in these cases was a switch from standard- to high-strength PERT. Before PERT dosing guidelines were established in 1995, more than 60 cases were reported worldwide.[83] Despite the voluntary withdrawal of high-strength formulations by manufacturers in early 1994, and the 1995 CF Consensus Conference recommendations that daily dosages should not exceed 10,000 IU lipase per kg body weight,[22] 37 cases of FC had been identified in the USA alone between 1995 and 1999.[84]

Early reports of FC in the USA led the CFF in collaboration with the FDA to perform a case-controlled study to investigate FC.[40] This and another case-control study showed a very strong association with the use of high doses of both standard- and high-strength PERT, usually over a prolonged period of time.[40,41] Other possible risk factors identified for FC in one case-controlled study included previous intestinal surgery, meconium ileus, distal intestinal obstruction syndrome, and use of H_2 receptor antagonists, corticosteroids, and recombinant human DNase.[40]

The underlying pathogenesis of FC remains unclear and mechanisms other than previous exposure to high doses of PERT are under discussion. According to the current literature, an association between FC and intake of methacrylic acid copolymer (Eudragit®, Evonik Röhm GmbH, Darmstadt, Germany) cannot be ruled out. This compound is sometimes a component of the enteric coating for drug products, including some PERT products and mesalazine.[81,85] In 2002, a review of the use of PERT products stated that the continued occurrence of FC in the CF population emphasized the need for close monitoring of PERT dosing and adherence in patients with CF.[86]

Although FC occurs predominantly in children, it has been reported in adults.[87-90] FC occurred in one adult with CF long after stopping high-dose enzyme preparations[90] and, rarely, has occurred even in the absence of PERT, suggesting that it might be a complication of CF, rather than just a result of PERT use.[91,92] In this context it should be noted that fibrosis of internal organs, particularly the pancreas, liver, and bile ducts, is inherent in the CF disease process,[93,94] and an increased prevalence of CF transmembrane receptor mutations has been found in patients with primary sclerosing cholangitis,[95] a disease characterized by progressive inflammation and fibrosis of the bile ducts. In a trans-abdominal ultrasound study assessing 83 patients with CF and 31 control subjects, a slight but significant gut wall thickening in both adults and children with CF was observed compared with controls.[96] There was no association of wall thickness with intake of high-strength enzymes, enzyme dosage, age, or sex. These findings are often mirrored in clinical practice in children with CF. Nevertheless, use of PERT at doses recommended by the CF consensus guidelines[21-24] remains essential for most patients with CF.

Overall, review of cumulative data and widespread exposure to CREON in the market suggests that FC is an extremely rare event, although continued monitoring is important. In line with a FDA requirement for all US-approved PERT products, the manufacturer of CREON will conduct a 10-year observational study looking at the incidence of and risk factors associated with FC in patients with CF in the USA (this is a class requirement for all PERT manufacturers).

Potential for Viral Transmission

The active ingredient of CREON, pancrelipase, is a mixture of digestive enzymes extracted from porcine pancreas glands harvested from pigs raised and slaughtered for food production. However, as with all porcine-derived PERT products, the possibility of contamination of the starting material with swine viruses capable of infecting humans has to be considered.

During manufacture, reduction of viral pathogens starts with meticulous sourcing of the raw material, specific measures to reduce the introduction of viruses into the raw material, and steps in the manufacturing process to inactivate or remove viral contaminants. In compliance with national and international guidelines for slaughterhouses, only pancreatic glands from animals released fit for human consumption are used. The manufacturing process is carried out according to Good Manufacturing Practices and complies with relevant guidelines.[97-99] Viral safety of the medicinal product is ensured by correct sourcing of the material, the validated manufacturing process, and testing of the active pharmaceutical ingredient (pancrelipase).

The pancrelipase manufacturing process is highly effective in inactivating enveloped viruses; however, it does not reduce all non-enveloped virus loads to the same extent. For non-enveloped viruses where contamination is a possibility, each virus is assessed individually as to the potential risk to patients. Testing is carried out for potentially zoonotic porcine viruses that may not be inactivated by the manufacturing process, with the rejection of positive batches.

Currently, the swine hepatitis E virus (HEV) is the only one of four non-enveloped viruses that is known to be zoonotic and could theoretically be a risk to humans. Previously, HEV infection in humans was thought to be primarily waterborne, occurring mainly in developing countries with poor sanitation. However, it is currently recognized that zoonotic transmission of HEV from swine and other animals can occur in both the developing and industrialized world. Swine HEV can be transmitted to humans by eating raw or undercooked swine livers and intestines, and by direct contact with infected animals.[100] Epidemiological data from blood donors in the USA and Europe show a seroprevalence for anti-HEV of 2%-21%.[101,102] In general, HEV causes a self-limiting disease and patients typically recover without sequelae within 2-4 weeks. Hepatitis E can present with the typical symptoms of viral hepatitis very similar to hepatitis A, but many cases are subclinical.[101,103] It was previously thought that HEV (mostly genotype 1) was associated with a high mortality rate in pregnant women, particularly in certain geographic areas; however, more recent studies and laboratory data suggest that this may not be the case.[100] In addition, humans are the natural host for genotype 1 and it does not infect swine.[100,103]

CREON clinical and safety databases have been reviewed to look for potential HEV cases. Taken together, no clinically relevant risk could be identified in terms of CREON intake and any liver diseases. In particular, no association between CREON and potential HEV infections could be established. Database review has limitations in risk detection; however, given that HEV is not found in pancreatic cells,[104] together with the implementation of appropriate mitigation steps for HEV contamination in the production process, it is considered unlikely that a causal relationship between CREON intake and HEV infection exists.

In summary, the manufacturer of CREON has instituted measures to minimize the potential for zoonotic agents in the source materials, inactivate many such agents that may be present, and screen the finished product for those considered potentially resistant to inactivation. In addition, no safety concern regarding unexplained viral illness has been identified with over 20 years' exposure history of CREON products. Therefore, the risk of viral illness associated with CREON is considered theoretical at the present time. As with any products derived from animal tissues, the potential risk for infectious disease due to the transmission of an infective agent cannot be totally excluded. In this light, the manufacturer will remain vigilant and will conduct a 10-year observational study to look at viral transmission of selected viruses in the CREON product, in line with the FDA requirement for all manufacturers of US-approved PERT products to carry out such studies.

CONCLUSION

PERT is the standard treatment for EPI. It remains essential in patients with CF to maintain adequate nutrition and normal growth status, and in some patients with CP or post-PS to prevent malnutrition and excessive weight loss. PERT products are available worldwide and are regulated in many countries, most recently in the USA following a FDA mandate for all PERT manufacturers to submit new drug applications. CREON has been available in Europe since 1984 and in the USA since 1987 in various formulations for the treatment of EPI; a new FDA-approved formulation of CREON is now available in the USA. Extensive clinical experience and clinical studies have confirmed the efficacy and safety of CREON in patients with CF, CP, and post-PS, including children aged <7 years. In clinical studies, consistent improvements in fat and nitrogen absorption, stool frequency, and clinical symptoms have been shown compared with placebo or baseline. CREON appears to be well tolerated regardless of patient age, with few withdrawals due to TEAEs and a low frequency of treatment-related TEAEs in clinical studies. No safety issues have been identified with the various CREON formulations based on global post-marketing surveillance data collected since 1984. As requested by the FDA, all PERT manufacturers in the USA are now carrying out studies to investigate further the incidence and risk factors associated with the rare gastrointestinal complication, FC, in patients with CF, and also the theoretical risk of viral transmission from porcine-derived PERT products; these studies will add to the existing evidence for a good safety profile of PERT products. Together the data suggest a very favorable risk-benefit profile for CREON in the treatment of EPI.

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REFERENCES

1. Layer P, Keller J. Pancreatic enzymes: secretion and luminal nutrient digestion in health and disease. J Clin Gastroenterol. 1999;28:3-10.

2. Konstan MW, Butler SM, Wohl ME, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. J Pediatr. 2003;142:624-630.

3. Steinkamp G, Wiedemann B. Relationship between nutritional status and lung function in cystic fibrosis: cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. Thorax. 2002;57:596-601.

4. Beker LT, Russek-Cohen E, Fink RJ. Stature as a prognostic factor in cystic fibrosis survival. J Am Diet Assoc. 2001;101:438-442.

5. Lai HC, Corey M, FitzSimmons S, Kosorok MR, Farrell PM. Comparison of growth status of patients with cystic fibrosis between the United States and Canada. Am J Clin Nutr. 1999;69:531-538.

6. United States Pharmacopoeial Convention. The United States Pharmacopeia 33. National Formulary 28 (USP 33-NF 28). Rockville, MD. United States Pharmacopoeial Convention. 2010.

7. DiMagno EP, Malagelada JR, Go VL, Moertel CG. Fate of orally ingested enzymes in pancreatic insufficiency. Comparison of two dosage schedules. N Engl J Med. 1977;296:1318-1322.

8. Hendeles L, Dorf A, Stecenko A, Weinberger M. Treatment failure after substitution of generic pancrelipase capsules. Correlation with in vitro lipase activity. JAMA. 1990;263:2459-2461.

9. DeYoung JL. Development of pancreatic enzyme microsphere technology and US findings with Pancrease in the treatment of chronic pancreatitis. Int J Pancreatol. 1989;5(suppl.):31-36.

10. Littlewood JM, Kelleher J, Walters MP, Johnson AW. In vivo and in vitro studies of microsphere pancreatic supplements. J Pediatr Gastroenterol Nutr. 1988;7(suppl 1.):S22-S29.

11. Walters MP, Littlewood JM. Pancreatin preparations used in the treatment of cystic fibrosis–lipase content and in vitro release. Aliment Pharmacol Ther. 1996;10:433-440.

12. Kuhn RJ, Eyting S, Henniges F, Potthoff A. In vitro comparison of physical parameters, enzyme activity, acid resistance, and pH dissolution characteristics of enteric-coated pancreatic enzyme preparations: implications for clinical variability and pharmacy substitution. J Pediatr Pharmacol Ther. 2007;12:115-128.

13. Kraisinger M, Hochhaus G, Stecenko A, Bowser E, Hendeles L. Clinical pharmacology of pancreatic enzymes in patients with cystic fibrosis and in vitro performance of microencapsulated formulations. J Clin Pharmacol. 1994;34:158-166.

14. Brady MS, Rickard K, Yu PL, Eigen H. Effectiveness and safety of small vs. large doses of enteric coated pancreatic enzymes in reducing steatorrhea in children with cystic fibrosis: a prospective randomized study. Pediatr Pulmonol. 1991;10:79-85.

15. Halm U, Löser C, Löhr M, Katschinski M, Mössner J. A double-blind, randomized, multicentre, crossover study to prove equivalence of pancreatin minimicrospheres versus microspheres in exocrine pancreatic insufficiency. Aliment Pharmacol Ther. 1999;13:951-957.

16. Santini B, Antonelli M, Battistini A, et al. Comparison of two enteric coated microsphere preparations in the treatment of pancreatic exocrine insufficiency caused by cystic fibrosis. Dig Liver Dis. 2000;32:406-411.

17. Stern RC, Eisenberg JD, Wagener JS, et al. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. Am J Gastroenterol. 2000;95:1932-1938.

18. Löhr JM, Hummel FM, Pirilis KT, Steinkamp G, Körner A, Henniges F. Properties of different pancreatin preparations used in pancreatic exocrine insufficiency. Eur J Gastroenterol Hepatol. 2009;21:1024-1031.

19. U.S. Food and Drug Administration. FDA news release; FDA requires pancreatic extract manufacturers to submit marketing applications. April 27, 2004. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108289.htm. Accessed July 14, 2010.

20. Abbott Laboratories. CREON® (pancrelipase) delayed-release capsules. Prescribing information. August, 2010. Available at: http://www.creon-us.com/default.htm. Accessed November 4, 2010.

21. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2002;35:246-259.

22. Borowitz DS, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. J Pediatr. 1995;127:681-684.

23. Sinaasappel M, Stern M, Littlewood J, et al. Nutrition in patients with cystic fibrosis: a European Consensus. J Cyst Fibros. 2002;1:51-75.

24. Borowitz D, Robinson KA, Rosenfeld M, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr. 2009;155:S73-S93.

25. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc. 2008;108:832-839.

26. Layer P, Keller J, Lankisch PG. Pancreatic enzyme replacement therapy. Curr Gastroenterol Rep. 2001;3:101-108.

27. Littlewood JM, Wolfe SP, Conway SP. Diagnosis and treatment of intestinal malabsorption in cystic fibrosis. Pediatr Pulmonol. 2006;41:35-49.

28. Kerem E, Corey M, Kerem BS, et al. The relation between genotype and phenotype in cystic fibrosis–analysis of the most common mutation (delta F508). N Engl J Med. 1990;323:1517-1522.

29. Walkowiak J, Sands D, Nowakowska A, et al. Early decline of pancreatic function in cystic fibrosis

patients with class 1 or 2 CFTR mutations. J Pediatr Gastroenterol Nutr. 2005;40:199-201.

30. Bronstein MN, Sokol RJ, Abman SH, et al. Pancreatic insufficiency, growth, and nutrition in infants identified by newborn screening as having cystic fibrosis. J Pediatr. 1992;120:533-540.

31. Southern KW, Munck A, Pollitt R, et al. A survey of newborn screening for cystic fibrosis in Europe. J Cyst Fibros. 2007;6:57-65.

32. Munck A, Dhondt JL, Sahler C, Roussey M. Implementation of the French nationwide cystic fibrosis newborn screening program. J Pediatr. 2008;153:228-233, 233 e221.

33. Davis PB. Cystic fibrosis since 1938. Am J Respir Crit Care Med. 2006;173:475-482.

34. Löser C, Möllgaard A, Fölsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. Gut. 1996;39:580-586.

35. Schneider A, Funk B, Caspary W, Stein J. Monoclonal versus polyclonal ELISA for assessment of fecal elastase concentration: pitfalls of a new assay. Clin Chem. 2005;51:1052-1054.

36. Wagner MH, Bowser EK, Sherman JM, Francisco MP, Theriaque D, Novak DA. Comparison of steatocrit and fat absorption in persons with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2002;35:202-205.

37. Van De Kamer JH, Ten Bokkel Huinink H, Weyers HA. Rapid method for the determination of fat in feces. J Biol Chem. 1949;177:347-355.

38. Farrell PM, Kosorok MR, Laxova A, et al. Nutritional benefits of neonatal screening for cystic fibrosis. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. N Engl J Med. 1997;337:963-969.

39. Assael BM, Casazza G, Iansa P, Volpi S, Milani S. Growth and long-term lung function in cystic fibrosis: a longitudinal study of patients diagnosed by neonatal screening. Pediatr Pulmonol. 2009;44:209-215.

40. FitzSimmons SC, Burkhart GA, Borowitz D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med. 1997;336:1283-1289.

41. Smyth RL, Ashby D, O'Hea U, et al. Fibrosing colonopathy in cystic fibrosis: results of a case-control study. Lancet. 1995;346:1247-1251.

42. Trapnell BC, Maguiness K, Graff GR, Boyd D, Beckmann K, Caras S. Efficacy and safety of Creon® 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros. 2009;8:370-377.

43. Graff GR, Maguiness K, McNamara J, et al. Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged 7 to 11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. Clin Ther. 2010;32:89-103.

44. Graff GR, McNamara J, Royall J, Caras S, Forssmann K. Safety and tolerability of a new formulation of pancrelipase delayed-release capsules (CREON®) in children under seven years of age with exocrine pancreatic insufficiency due to cystic fibrosis: an open-label, multicentre, single-treatment-arm study. Clin Drug Investig. 2010;30:351-364.

45. Colombo C, Fredella C, Russo MC, et al. Efficacy and tolerability of Creon for Children in infants and toddlers with pancreatic exocrine insufficiency caused by cystic fibrosis: an open-label, single-arm, multicenter study. Pancreas. 2009;38:693-699.

46. Munck A, Duhamel JF, Lamireau T, et al. Pancreatic enzyme replacement therapy for young cystic fibrosis patients. J Cyst Fibros. 2009;8:14-18.

47. Patchell CJ, Desai M, Weller PH, et al. Creon® 10,000 Minimicrospheres™ vs. Creon® 8,000 microspheres–an open randomised crossover preference study. J Cyst Fibros. 2002;1:287-291.

48. Borowitz D, Konstan MW, O'Rourke MS, Cohen M, Hendeles L, Murray FT. Coefficients of fat and nitrogen absorption in healthy subjects and individuals with cystic fibrosis. J Pediatr Pharmacol Ther. 2007;12:47-52.

49. Solvay Pharmaceuticals. CREON® (pancrelipase delayed-release capsules). FDA Antiviral Drugs Advisory Committee. 2008. Available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4402b1-03-SOLVAY.pdf. Accessed July 14, 2010.

50. Marks IN, Banks S. Chronic pancreatitis. Etiology, clinical aspects, and medical management. In: Berk JE, Haubrich WS, Kalser MH, Roth JLA, Schaffner F, eds. Bockus Gastroenterology. Vol. 6. Philadelphia: W.B. Saunders; 1985:4020-4040.

51. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med. 2009;169:1035-1045.

52. Whitcomb DC. Genetic predisposition to alcoholic chronic pancreatitis. Pancreas. 2003;27:321-326.

53. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120:682-707.

54. Van Hoozen CM, Peeke PG, Taubeneck M, Frey CF, Halsted CH. Efficacy of enzyme supplementation after surgery for chronic pancreatitis. Pancreas. 1997;14:174-180.

55. Domínguez-Muñoz JE, Iglesias-García J. Oral pancreatic enzyme substitution therapy in chronic pancreatitis: is clinical response an appropriate marker for evaluation of therapeutic efficacy? J Pancreas (Online). 2010;11:158-162.

56. DiMagno EP, Go VL, Summerskill WH. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. N Engl J Med. 1973;288:813-815.

57. Lankisch PG, Lembcke B, Wemken G, Creutzfeldt W. Functional reserve capacity of the exocrine pancreas. Digestion. 1986;35:175-181.

58. Carrière F, Grandval P, Gregory PC, et al. Does the pancreas really produce much more lipase than required for fat digestion? J Pancreas (Online). 2005;6:206-215.

59. Dutta SK, Bustin MP, Russell RM, Costa BS. Deficiency of fat-soluble vitamins in treated patients with pancreatic insufficiency. Ann Intern Med. 1982;97:549-552.

60. Marotta F, Labadarios D, Frazer L, Girdwood A, Marks IN. Fat-soluble vitamin concentration in chronic alcohol-induced pancreatitis. Relationship with steatorrhea. Dig Dis Sci. 1994;39:993-998.

61. Nakamura T, Takebe K, Imamura K, et al. Fat-soluble vitamins in patients with chronic pancreatitis (pancreatic insufficiency). Acta Gastroenterol Belg. 1996;59:10-14.

62. Bang Jørgensen B, Thorsgaard Pedersen N, Worning H. Short report: lipid and vitamin B12 malassimilation in pancreatic insufficiency. Aliment Pharmacol Ther. 1991;5:207-210.

63. Haaber AB, Rosenfalck AM, Hansen B, Hilsted J, Larsen S. Bone mineral metabolism, bone mineral density, and body composition in patients with chronic pancreatitis and pancreatic exocrine insufficiency. Int J Pancreatol. 2000;27:21-27.

64. Mann ST, Stracke H, Lange U, Klör HU, Teichmann J. Alterations of bone mineral density and bone metabolism in patients with various grades of chronic pancreatitis. Metabolism. 2003;52:579-585.

65. Morán CE, Sosa EG, Martinez SM, et al. Bone mineral density in patients with pancreatic insufficiency and steatorrhea. Am J Gastroenterol. 1997;92:867-871.

66. Domínguez-Muñoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. Curr Gastroenterol Rep. 2007;9:116-122.

67. Domínguez-Muñoz JE, Iglesias-García J, Iglesias-Rey M, Figueiras A, Vilariño-Insua M. Effect of the administration schedule on the therapeutic efficacy of oral pancreatic enzyme supplements in patients with exocrine pancreatic insufficiency: a randomized, three-way crossover study. Aliment Pharmacol Ther. 2005;21:993-1000.

68. Guarner L, Rodríguez R, Guarner F, Malagelada JR. Fate of oral enzymes in pancreatic insufficiency. Gut. 1993;34:708-712.

69. O'Keefe SJ, Cariem AK, Levy M. The exacerbation of pancreatic endocrine dysfunction by potent pancreatic exocrine supplements in patients with chronic pancreatitis. J Clin Gastroenterol. 2001;32:319-323.

70. Safdi M, Bekal PK, Martin S, Saeed ZA, Burton F, Toskes PP. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. Pancreas. 2006;33:156-162.

71. Whitcomb DC, Lehman GA, Vasileva G, et al. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: a double-blind randomized trial. Am J Gastroenterol. 2010;105:2276-2286.

72. Czakó L, Takács T, Hegyi P, et al. Quality of life assessment after pancreatic enzyme replacement therapy in chronic pancreatitis. Can J Gastroenterol. 2003;17:597-603.

73. Borowitz D, Durie PR, Clarke LL, et al. Gastrointestinal outcomes and confounders in cystic fibrosis. J Pediatr Gastroenterol Nutr. 2005;41:273-285.

74. Dutta SK, Hlasko J. Dietary fiber in pancreatic disease: effect of high fiber diet on fat malabsorption in pancreatic insufficiency and in vitro study of the interaction of dietary fiber with pancreatic enzymes. Am J Clin Nutr. 1985;41:517-525.

75. Graham DY, Sackman JW. Mechanism of increase in steatorrhea with calcium and magnesium in exocrine pancreatic insufficiency: an animal model. Gastroenterology. 1982;83:638-644.

76. Proesmans M, De Boeck K. Omeprazole, a proton pump inhibitor, improves residual steatorrhoea in cystic fibrosis patients treated with high dose pancreatic enzymes. Eur J Pediatr. 2003;162:760-763.

77. Domínguez-Muñoz JE, Iglesias-García J, Iglesias-Rey M, Vilariño-Insua M. Optimising the therapy of exocrine pancreatic insufficiency by the association of a proton pump inhibitor to enteric coated pancreatic extracts. Gut. 2006;55:1056-1057.

78. Bruno MJ, Rauws EA, Hoek FJ, Tytgat GN. Comparative effects of adjuvant cimetidine and omeprazole during pancreatic enzyme replacement therapy. Dig Dis Sci. 1994;39:988-992.

79. Reichard KW, Vinocur CD, Franco M, et al. Fibrosing colonopathy in children with cystic fibrosis. J Pediatr Surg. 1997;32:237-241.

80. Littlewood JM. Update on intestinal strictures. J R Soc Med. 1999;92 Suppl 37:41-49.

81. Bakowski MT, Prescott P. Patterns of use of pancreatic enzyme supplements in fibrosing colonopathy: implications for pathogenesis. Pharmacoepidemiol Drug Saf. 1997;6:347-358.

82. Smyth RL, van Velzen D, Smyth AR, Lloyd DA, Heaf DP. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. Lancet. 1994;343:85-86.

83. Lloyd-Still JD, Beno DW, Kimura RM. Cystic fibrosis colonopathy. Curr Gastroenterol Rep. 1999;1:231-237.

84. Stevens J, Davis M, Pawel B, et al. Fibrosing colonopathy (FC)–a retrospective analysis of U.S. cases 1995-1999. Pediatr Pulmonol. 2001;32(S22):344.

85. Prieto G, Pérez-Moneo B, Molina M, et al. Fibrosing colonopathy associated with treatment with enteric-coated mesalazine pills. Inflamm Bowel Dis. 2009;15:1452-1453.

86. Schibli S, Durie PR, Tullis ED. Proper usage of pancreatic enzymes. Curr Opin Pulm Med. 2002;8:542-546.

87. Bansi DS, Price A, Russell C, Sarner M. Fibrosing colonopathy in an adult owing to over use of pancreatic enzyme supplements. Gut. 2000;46:283-285.

88. Brett AS, Mack EH. Fibrosing colonopathy in adults with cystic fibrosis. AJR Am J Roentgenol. 2008;190:W73.

89. Häusler M, Meilicke R, Biesterfeld S, Heimann G. First adult patient with fibrosing colonopathy. Am J Gastroenterol. 1998;93:1171-1172.

90. Mack EH, Brett AS, Brown D. Fibrosing colonopathy in an adult cystic fibrosis patient after discontinuing pancreatic enzyme therapy. South Med J. 2004;97:901-904.

91. Franzen D, Went P, Buhlmann U. Fibrosing colonopathy in absence of pancreatic enzyme supplementation in one adult patient with cystic fibrosis. Indian J Gastroenterol. 2008;27:133-134.

92. Waters BL. Cystic fibrosis with fibrosing colonopathy in the absence of pancreatic enzymes. Pediatr Dev Pathol. 1998;1:74-78.

93. Robertson MB, Choe KA, Joseph PM. Review of the abdominal manifestations of cystic fibrosis in the adult patient. Radiographics. 2006;26:679-690.

94. Agrons GA, Corse WR, Markowitz RI, Suarez ES, Perry DR. Gastrointestinal manifestations of cystic fibrosis: radiologic-pathologic correlation. Radiographics. 1996;16:871-893.

95. Sheth S, Shea JC, Bishop MD, et al. Increased prevalence of CFTR mutations and variants and decreased chloride secretion in primary sclerosing cholangitis. Hum Genet. 2003;113:286-292.

96. Dialer I, Hundt C, Bertele-Harms RM, Harms HK. Sonographic evaluation of bowel wall thickness in patients with cystic fibrosis. J Clin Gastroenterol. 2003;37:55-60.

97. Center for Drug Evaluation and Research, U.S. Department of Health and Human Services Food and Drug Administration. Guidance for industry. Exocrine pancreatic insufficiency drug products–submitting NDAs. April 2006. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf. Accessed July 14, 2010.

98. Committee for Proprietary Medicinal Products (CPMP). Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses (CPMP/BWP/268/95). February 14, 1996. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000351.jsp&mid=WC0b01ac058002956c&murl=menus/regulations/regulations.jsp&jsenabled=true. Accessed July 14, 2010.

99. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Viral safety

evaluation of biotechnology products derived from cell lines of human or animal origin Q5A (R1). 1999. Available at: http://www.ich.org/cache/compo/363-272-1.html#Q5A. Accessed July 14, 2010.

100. Meng XJ. Recent advances in hepatitis E virus. J Viral Hepat. 2010;17:153-161.

101. Pavio N, Renou C, Di Liberto G, Boutrouille A, Eloit M. Hepatitis E: a curious zoonosis. Front Biosci. 2008;13:7172-7183.

102. Mushahwar IK. Hepatitis E virus: molecular virology, clinical features, diagnosis, transmission, epidemiology, and prevention. J Med Virol. 2008;80:646-658.

103. Meng XJ. Hepatitis E virus: animal reservoirs and zoonotic risk. Vet Microbiol. 2010;140:256-265.

104. Williams TP, Kasorndorkbua C, Halbur PG, et al. Evidence of extrahepatic sites of replication of the hepatitis E virus in a swine model. J Clin Microbiol. 2001;39:3040-3046.

ORIGINAL RESEARCH ARTICLE

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Safety and Tolerability of a New Formulation of Pancrelipase Delayed-Release Capsules (CREON®) in Children Under Seven Years of Age with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis

An Open-Label, Multicentre, Single-Treatment-Arm Study

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Abstract

Background: Exocrine pancreatic insufficiency (EPI) is a deficiency of digestive enzymes caused by diseases such as cystic fibrosis (CF). Patients with EPI due to CF require pancreatic enzyme replacement therapy (PERT) in order to maintain adequate nutrition. A new formulation of pancrelipase delayed-release capsules (CREON®) recently received US FDA approval and has demonstrated efficacy and safety in patients with CF aged ≥7 years.

Objectives: The objectives of this study were to observe the safety and tolerability of new formulation pancrelipase delayed-release capsules (study drug) versus the standard of care PERT (standard therapy) in children aged <7 years with CF and EPI. Secondary objectives were to assess the ease of accurate dosing of study drug, monitor clinical symptoms and compare the efficacy of both treatments.

Methods: This was an open-label, multicentre, single-treatment-arm study in children aged <7 years with a confirmed diagnosis of CF and EPI. After the screening period (approximately 14 days), all patients entered a 3-day assessment period on their usual PERT (standard therapy), followed by the study drug treatment phase (10–14 days; target dose 8000 lipase units/kg bodyweight/day), which included a second 3-day assessment period. The safety and tolerability of both treatments were documented by recording adverse events (AEs). Clinical symptoms (mean daily stool frequency,

abdominal pain, stool consistency and flatulence) were monitored and ease of accurate dosing, as judged by caregivers, was reported. Efficacy was determined by comparison of percent stool fat in spot stool samples collected during both 3-day assessment periods.
Results: Of the 19 patients who had informed consent from their parent/legally acceptable representative, one was withdrawn as a screen failure and was excluded from the safety and efficacy analyses; thus, 18 patients completed the study. The median age (range) was 23 (4–71) months and 13 (72%) were male. During study drug treatment, patients received a mean ± SD dose in lipase units/kg bodyweight/day of 7542 ± 1335 versus 6966 ± 3392 on standard therapy. Overall, nine (50%) patients had at least one treatment-emergent AE (TEAE) whilst receiving either treatment. All TEAEs in this study were reported as mild and none resulted in patient discontinuation. The caregivers had a slight preference for study drug over standard therapy in terms of ease of accurate dosing: six (33.3%) caregivers thought the study drug was easier to dose while only one (5.6%) thought the study drug was harder to dose than standard therapy. Clinical symptom assessment results were similar between treatments. There was no clinically meaningful difference (significance not tested) between study drug and standard therapy in the mean ± SD percent of stool fat: 28.1 ± 9.9 and 27.9 ± 8.9, respectively.
Conclusion: In this study in children aged <7 years with EPI due to CF, the new formulation pancrelipase delayed-release capsules (CREON®) were clinically comparable with standard therapy in terms of safety, tolerability and efficacy.

Introduction

Exocrine pancreatic insufficiency (EPI) is an inability to digest food adequately secondary to a lack of digestive enzymes secreted by the pancreas. It has multiple causes but is most commonly seen in cystic fibrosis (CF)[1-3] and chronic pancreatitis (CP).[4-6] The symptoms of EPI include steatorrhoea, diarrhoea, abdominal pain and excess flatulence, and the disorder can lead to a deficiency of fat-soluble vitamins and ultimately malnutrition and a failure to thrive in children.[7] Most patients with CF suffer from EPI from birth.[8]

Better nutritional status in CF correlates with better pulmonary function and improved survival.[9] Patients with CF have increased caloric needs compared with non-CF individuals because of a higher basal metabolic rate and loss of ingested calories due to maldigestion.[9] Therefore, effective treatment of EPI is essential to ensure optimal growth status in children and maintain adequate nutrition status in adults.[9] EPI is generally treated with pancreatic enzyme replacement therapy (PERT),[1] and the correct dosing of PERT is critical for the effective treatment of EPI and to avoid potential complications such as fibrosing colonopathy.[10] Consensus-based guidelines recommend that PERT dosing should begin with 1000 lipase units/kg bodyweight/meal for children aged <4 years and with 500 lipase units/kg bodyweight/meal for those aged >4 years.[9,11] The recommended dosing range for children and adults is 500–2500 lipase units/kg bodyweight/meal not exceeding a total of 10 000 lipase units/kg bodyweight/day.[9]

Enteric-coated formulations were developed to protect PERT preparations during passage through the stomach because, in powder form, conventional formulations are rapidly inactivated by gastric acid.[12] Enteric coatings are frequently used in many medicinal products, for example with proton pump inhibitors to protect the active ingredient from gastric acid and with aspirin (acetylsalicylic acid) to protect the stomach from the active ingredient. PERT is delivered as enteric-coated microspheres, administered in gelatin capsules that dissolve in the stomach, thus allowing release of enzymes in the duodenum at a favourable intestinal pH (≥5.5). Studies have shown that these delayed-release formulations improve fat absorption compared with conventional formulations.[13-17]

For over 20 years, porcine-derived pancrelipase (pancreatin) delayed-release capsules, United States Pharmacopeia (CREON®, Solvay Pharmaceuticals, Inc. [now part of Abbott], Marietta, GA, USA), have provided essential PERT for treating maldigestion due to EPI. Historically, the efficacy and safety of pancrelipase in CF[18] and CP[19] patients with EPI have been reported in placebo-controlled studies. In addition, the results of an open-label study[20] and a randomized study[21] that investigated pancrelipase in very young infants (aged <3 years) with EPI due to CF have been published. For many years, PERT products in the US were on the market, but not approved. In addition, PERT products previously on the market had varying degrees of enzyme overfill to account for product decomposition. As a result, the labelled lipase content was not necessarily the actual lipase content. This could make for difficulties titrating some patients on PERT. Therefore, the US FDA mandated that all PERT products require evidence regarding efficacy and safety shown in well designed clinical studies and that the lipase content on the label is consistent and accurate.[22]

A new formulation of pancrelipase delayed-release capsules (CREON® 6000-, 12 000- or 24 000-lipase unit capsules; Solvay Pharmaceuticals, Inc. [now part of Abbott]) has recently been approved by the FDA for the treatment of EPI. These capsules contain enteric-coated pancrelipase spheres (0.7–1.6 mm in diameter) for oral administration.[23] *In vitro* studies investigating enzyme activity, gastric resistance and dissolution profiles have shown that new formulation pancrelipase delayed-release capsules are pharmaceutically comparable to previous formulations.[24] FDA approval was primarily based on the results of a randomized, double-blind, crossover, placebo-controlled study, which reported that pancrelipase delayed-release 24 000-lipase unit capsules had greater efficacy than placebo in improving primarily fat and protein digestion and clinical symptoms in patients aged ≥12 years with EPI due to CF.[25] Studies of this new formulation pancrelipase have also been conducted in the paediatric population in CF patients with EPI. A randomized, double-blind, two-period, crossover, placebo-controlled, multicentre study reported that pancrelipase delayed-release 12 000-lipase unit capsules were effective and safe in patients aged 7–11 years with EPI due to CF.[26]

In this publication we report the results of an open-label, multicentre study assessing the safety and tolerability of new formulation pancrelipase delayed-release capsules in infants and children aged <7 years with EPI due to CF. This study design differed from the previous studies in that it was not randomized, double-blind or placebo-controlled, as such a design posed risks to the vulnerable population investigated. The main objective was to address the safety of the new formulation in the younger paediatric population. Secondary objectives were to assess the ease of accurate dosing of pancrelipase, and efficacy using spot stool fat measurements. An open-label design was used for this study due to the difficulty in blinding the pancrelipase/standard therapy products. This is the first reported study of the new formulation of pancrelipase delayed-release capsules in a paediatric population aged <7 years.

Patients and Methods

This was an open-label, multicentre, single-treatment-arm study to assess the safety and tolerability of a new formulation of pancrelipase delayed-release capsules (study drug) in infants and children aged <7 years with a confirmed diagnosis of CF and EPI. It was performed at nine centres across the US between 15 April 2009 and 29 June 2009 (study number NCT00775528). The study was conducted in compliance with

Good Clinical Practice and applicable national regulations, and was approved by the Institutional Review Board/Independent Ethics Committee at each site.

Objectives

The objectives of this study were to observe the safety and tolerability profile of the study drug compared with the standard therapy that the patients were receiving at study enrolment. The safety objectives were to assess short-term safety and tolerability, with the following measurements obtained: vital signs; bodyweight; physical examination findings; and recording of adverse events (AEs). The secondary study objectives were to assess the ease of accurate dosing of study drug compared with standard therapy and to compare efficacy with regard to the percent fat from spot stool samples collected during two 3-day assessment periods. This was an exploratory study to test the hypothesis that the study drug would be clinically comparable with standard therapy.

Study Design

The study design is shown in figure 1. During the screening visit, patients were evaluated for their eligibility to enrol in the study while remaining on all of their usual therapies and their standard PERT. Assessments performed at screening included a physical examination (height, bodyweight and oral mucosa examination), measurement of vital signs, measurement of pancreatic faecal elastase (if not performed within the previous 12 months) and a review of the patient's medical history, concomitant medication and demographic data. Eligible patients continued on the same dose of standard therapy and entered the first 3-day assessment, which was performed 3 days prior to baseline and involved clinical symptom assessment and recording of dietary and fat intake, enzyme dosing and AEs. Stool frequency was also recorded and at least one complete bowel movement was collected on each of the 3 days to enable measurement of percent stool fat. At baseline, bodyweight, vital signs, concomitant medication and AEs were recorded in order to monitor any changes occurring since screening. The following day, all patients received study drug in the treatment phase of the study, which lasted 10–14 days. Three days before the end of treatment, a second 3-day assessment period was scheduled; during this time the same parameters as measured while patients were on standard

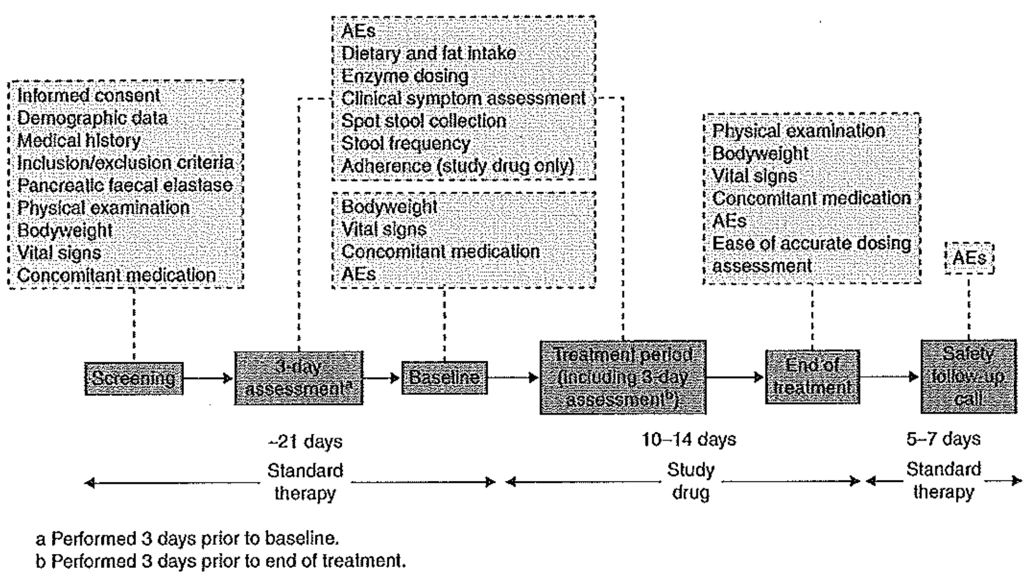

Fig. 1. Study design. **AE** = adverse event.

therapy were evaluated for patients receiving study drug. Ease of accurate dosing was assessed at the end of treatment along with a physical examination, evaluation of vital signs and a review of concomitant medication and AEs. Following the end of treatment, patients resumed their standard therapy and received a follow-up safety phone call for an update on any AEs 5–7 days later. This study was performed while patients continued taking all of their usual CF therapies at home. Stool samples were generally collected at home and patients visited the clinics/research units to undergo examinations.

Patients

Written informed consent signed by the patient's parents or legally acceptable representative was required at screening before any study-related procedures were performed. A confirmed diagnosis of CF by two sweat chloride tests >60 mEq/L or gene analysis with two known CF-causing mutations was necessary for all patients. EPI was established by a human faecal elastase value of <50 μg/g stool, measured within the past 12 months. Patients were required to be aged 1 month to <7 years and weigh a minimum of 3.75 kg. Patients were also required to be receiving treatment with a commercially available PERT product (no limitations on the type of PERT used were applied) at a stable dose and have a clinically stable condition without evidence of acute respiratory disease or any other acute condition. Patients were excluded if they had severe medical conditions that might limit participation in or completion of the study, or if they had recently undergone major surgery (excluding appendicectomy). Also excluded were patients with: a history of fibrosing colonopathy or distal ileal obstruction syndrome; ileus or acute abdomen; malignancy in the digestive tract; HIV infection; a medical need for the use of immunosuppressive drugs; known allergy to pancrelipase (pancreatin) or the inactive ingredients of pancrelipase delayed-release capsules; or exposure to an experimental drug within 30 days of the study start. Patients were also excluded if they were believed to be at risk from caregiver non-adherence or an inability to complete the study as designed.

Intake of any oral pancreatic enzyme preparation in addition to the study medication was not permitted during the study; however, PERT prescribed as part of the patient's standard medical care (standard therapy) was taken until the start of study drug treatment. Concomitant medications including stomach acid reducers, gastrointestinal tract motility agents or bile secretion modulators could be used, providing the medication was commercially available and was prescribed according to the recommended dose. It was necessary for the medication to be taken by the patient for at least 4 weeks prior to the study start, at a stable dose with no dosing changes allowed during the course of the study. During the study, all medication taken by the patient, except for the study drug, was recorded on a concomitant medication form.

Treatment

The patients received standard therapy at their usual dose until the day after the baseline assessments were performed. The study drug was given as 3000-, 6000- and 12 000-lipase unit capsules and the correct number of capsules to be consumed was calculated to provide 8000 lipase units/kg bodyweight/day without exceeding the maximum lipase dose of 10 000 lipase units/kg bodyweight/day. Patients who were on a higher lipase dose before the study were treated with this dose providing it did not exceed 10 000 lipase units/kg bodyweight/day. The targeted dose was within the recommended range according to consensus CF guidelines.[9,11] The study drug was administered in divided doses with meals. Capsule contents were sprinkled onto apple sauce if the patients could not swallow the capsules. Partial capsule doses were not permitted for study drug treatment; however, if a patient was using partial doses of standard therapy capsules this was continued during the study. The combination of capsule strengths needed to achieve accurate dosing based on the patient's weight, caloric requirements, number of meals and meal fat content consumed each day was determined by the study site and caregiver together. Patients were considered adherent if the mean daily study drug dose for the 3-day assessment period was at least 6400 lipase units/kg bodyweight. Adherence was assessed by comparing the quantity of unused, partly used or empty bottles returned to the investigator against the dosing regimen of 8000 lipase units/kg bodyweight/day at each visit.

Safety Evaluation

Safety measures included recording of AEs according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, measuring vital signs and physical examination. For standard therapy, AEs that started at or after screening but before the first dose of study drug were recorded; for study drug, AEs were recorded with a start date on or after the date of first study drug dose but within 1 day after the last dose of study drug.

Bodyweight was recorded in triplicate using a calibrated scale at screening, baseline and at the end of treatment according to the standardized procedure 'Body Weight Process' in the study manual provided to each site. Mean values were recorded; available values were used if it was not possible to obtain all three measurements.

Outcomes and Efficacy Assessments

Patients received a normal home diet, and the food consumed during both 3-day assessment periods was recorded by the caregiver in the form of a dietary diary. Home enzyme dosing for PERT during both 3-day assessment periods was recorded in a pancreatic supplement diary by the caregiver. Caregivers were instructed to maintain a diet during the study drug treatment phase as close as possible to that of the screening period.

At the end of treatment, investigators asked the caregivers to provide their opinion on the ease of accurate study drug dosing compared with the standard home therapy (standard therapy) based on the following scale: easier than standard therapy; the same as standard therapy; and harder than standard therapy.

Clinical symptom assessment was performed in the evenings of each of the 3-day assessment periods. The parameters assessed were: stool frequency (number per day); stool consistency (0 = hard, 1 = formed/normal, 2 = soft, 3 = watery); flatulence (0 = none, 1 = mild, 2 = moderate, 3 = severe); and abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe). Scores were recorded in a clinical symptom assessment diary by the caregiver. Abdominal pain was assessed in a verbal manner only in patients capable of discriminating intensity in an accurate manner. Therefore, not all patients were assessed for abdominal pain and the investigator decided at screening whether this symptom should be measured in each individual patient.

At least one complete bowel movement was required to be collected on each of the 3 days of the assessment periods but caregivers were instructed to collect as many as possible for the stool fat analysis. Stool fat analysis was performed by Mayo Clinical Trial Services, Rochester, MN, USA using validated methods.[27] The stool fat content was calculated for each patient during each assessment period and expressed as fat percent of dry solid weight per bowel movement. The mean daily fat and calorie intake was calculated by the site dietician using standard resources based on the quantity and type of food consumed.

Statistical Methods

The safety sample consisted of patients with informed consent who had received at least one dose of study drug, and was used for the analysis of safety data. AEs were reported on a per-patient basis. All other analyses were performed on the full analysis sample, which consisted of patients who were included in the safety sample and had data for at least one post-baseline assessment. The baseline period was defined as the period from informed consent to the first study drug administration, and the baseline value was defined as the last non-missing value collected before the first study drug administration. The endpoint value for treatment was defined as the last non-missing value assigned to that treatment for the patient. Percentiles and Z-scores at screening were calculated for predicted height, bodyweight and body mass index (BMI) according to Centers for Disease Control (CDC) standards for the healthy paediatric population.[28,29] Efficacy was determined by comparison of standard therapy and study drug in terms of percent fat content of spot stool samples collected during the two 3-day assessment periods. The fat content of stool samples, clinical symptom assessment and ease of accurate dosing variables were summarized by standard descriptive methods. No inferential statistical analyses were performed for this study.

Sample Size

This was a descriptive and exploratory study; the sample size of 18 patients was not based on a statistical power calculation. Five sub-groups based on patients' age were defined for enrolment purposes: 1–6 months; >6–12 months; >12–24 months; >24–48 months; and >48 months to <84 months of age. At least three patients were enrolled in each age sub-group with no more than four patients in any group.

Table I. Patient demographics and characteristics at screening[a,b]

Variable	All patients (n=18)
Age, mo [median (range)]	23.0 (4–71)
Males [n (%)]	13 (72)
Race	
White [n (%)]	18 (100)
Height (m)	0.86±0.17
percentile predicted height by age	53.4±30.1
Z-score predicted height by age	0.13±0.95
Bodyweight (kg)	12.2±4.6
percentile predicted bodyweight by age	42.7±25.0
Z-score predicted bodyweight by age	−0.28±0.98
BMI[c] (kg/m²)	16.1±1.5
percentile predicted BMI[c] by age	52.6±27.4
Z-score predicted BMI[c] by age	0.10±0.87

a Values are expressed as mean±SD unless otherwise specified.

b Percentiles and Z-scores were calculated according to the Centers for Disease Control standards for the healthy paediatric population.[28,29]

c n=9 (BMI not measured for children aged <2 years).

BMI = body mass index.

Results

Demographics and characteristics at screening for patients who received the study drug are shown in table I. Of the 19 patients who had informed consent from their parent/legally acceptable representative, one patient failed screening (due to faecal elastase above the inclusion criterion limit); therefore 18 patients were enrolled. The median age (range) was 23 (4–71) months and the patients were predominantly male (13/18; 72%). All patients had either a current or historical (within 12 months) faecal elastase value of <50 μg/g stool. At screening, all patients provided a full medical history and of note were two patients (11.1%) with *Pseudomonas aeruginosa* colonization in their respiratory tract and five patients (27.8%) with a history of meconium ileus at birth.

To assess any changes that may have occurred from screening to baseline while on standard therapy, the patients' weight and BMI were measured again at baseline and remained relatively stable: mean±SD weight 12.3±4.5 kg and mean±SD BMI 16.4±1.4 kg/m². Percentiles and Z-scores calculated for predicted height, weight and BMI according to CDC standards for the healthy paediatric population are shown in table I. Concomitant medication was assessed throughout the study. During both the standard therapy and study drug periods eight patients (44%) were on acid-suppressing medication and one patient (5.6%) was on the gastric motility agent metoclopramide.

During the 3-day study drug assessment period, 14 patients (77.8%) were considered adherent to the study medication (i.e. they received at least 6400 lipase units/kg bodyweight/day). During the entire 12-day dispensing period, 83.3% of patients were 80–120% adherent to the study drug treatment, and the overall mean adherence was 97.2%. One patient exceeded the protocol-defined maximum daily dose of 10 000 lipase units/kg bodyweight, and had a mean daily dose of 11 064 lipase units/kg bodyweight during the 3-day study drug assessment period. There was a greater exposure to standard therapy versus study drug during the study as there was a longer treatment period due to the prolonged screening phase: mean±SD number of days exposed to treatment 18.2±4.9 versus 12.6±1.2 (table II).

During the 3-day assessment periods, a slightly lower mean±SD dose in lipase units/kg bodyweight/day was received on standard therapy compared with study drug: 6966±3392 versus 7542±1335. However, the mean±SD doses received on standard therapy compared with study drug in lipase units/g fat intake/day were similar: 2366±1772 and 2432±1495, respectively. The standard therapy dose distribution in lipase units/kg bodyweight/day was more skewed than that of study drug with median values of 6066 and 7538, respectively. Nevertheless, the actual dose received for study drug was close to the targeted dose of 8000 lipase units/kg bodyweight/day. It should be noted that during the standard therapy phase patients received their usual standard therapy at their usual dose and the use of partial capsules was permitted.

Safety and Tolerability

All TEAEs are listed in table III. Overall, nine patients (50%) had at least one TEAE during each treatment phase. No patients discontinued the study due to TEAEs. The only TEAE judged possibly related to treatment by the investigator at the site was a diaper rash in one patient occurring during the study drug treatment phase. All TEAEs in both treatment groups were judged by investigators to be mild in severity. No serious AEs occurred and there were no deaths.

Clinical symptom assessment (abdominal pain, stool consistency and flatulence) and mean daily stool frequency during each 3-day assessment period on study drug and standard therapy suggested clinical equivalence for both treatments (figures 2 and 3). There was slightly more day-to-day variability (significance not tested) in mean daily stool frequency when patients were receiving standard therapy compared with study drug.

Vital signs remained relatively stable from the beginning to the end of the assessment periods for both study drug and standard therapy. Bodyweight and BMI data are shown in table IV.

Ease of Accurate Dosing

Ease of accurate dosing on study drug was assessed by the caregivers at the end of treatment and the data appeared to show a slight preference for study drug over standard therapy (table II).

Efficacy

The study drug and standard therapy were clinically equivalent in terms of fat absorption: mean±SD spot stool fat percent values obtained during the 3-day assessment periods were 28.1±9.9 and 27.9±8.9, respectively (table V). Fat intake and total calorie intake were similar

Table II. Duration and treatment dose for study drug and standard therapy and ease of accurate dosing of study drug

Variable	Study drug (n=18)	Standard therapy (n=18)
Duration of exposure to treatment (mean±SD)		
number of days	12.6±1.2	18.2±4.9
Dose[a] (mean±SD)		
lipase units/kg bodyweight/day	7542±1335	6966±3392
lipase units/g fat intake/day	2432±1495	2366±1772
Ease of accurate dosing[b] [n (%)]		
easier than standard therapy	6 (33.3)	N/A
same as standard therapy	11 (61.1)	N/A
harder than standard therapy	1 (5.6)	N/A

a Measured during each 3-day assessment period.

b Assessed by caregiver at end of study drug treatment.

N/A = not applicable.

Table III. Incidence of all treatment-emergent adverse events (TEAEs)[a]

Adverse event	Study drug (n = 18)	Standard therapy (n = 18)
Any TEAE	9 (50)	9 (50)
Serious TEAE	0	0
Discontinuation due to TEAE	0	0
Severe TEAE	0	0
Treatment-related TEAE	1 (5.6)	0
Eye disorders	0	1 (5.6)
conjunctivitis	0	1 (5.6)
Gastrointestinal disorders	2 (11.1)	2 (11.1)
teething	0	1 (5.6)
diarrhoea	1 (5.6)	0
abdominal pain, upper	0	1 (5.6)
vomiting	1 (5.6)	0
General disorders	2 (11.1)	2 (11.1)
pyrexia	1 (5.6)	2 (11.1)
irritability	1 (5.6)	0
Infections and infestations	5 (27.8)	4 (22.2)
skin *Candida*	1 (5.6)	0
otitis media[b]	3 (16.7)	1 (5.6)
otitis media, acute	1 (5.6)	1 (5.6)
bronchitis	1 (5.6)	0
upper respiratory tract infection	0	2 (11.1)
viral infection	0	1 (5.6)
Metabolism and nutrition disorders	1 (5.6)	0
decreased appetite	1 (5.6)	0
Respiratory, thoracic and mediastinal disorders	2 (11.1)	3 (16.7)
cough	2 (11.1)	2 (11.1)
rhinorrhoea	1 (5.6)	1 (5.6)
Skin and subcutaneous tissue disorders	1 (5.6)	1 (5.6)
dermatitis, diaper	1 (5.6)[c]	1 (5.6)

a Values are expressed as no. (%) of patients.

b Only one patient experienced the same TEAE of otitis media (at the MedDRA preferred term level) on both study drug and standard therapy; however, these events were originally coded differently by the investigator as right otitis media and bilateral otitis media, respectively.

c TEAE considered possibly related to study drug treatment as judged by investigator.

during the study drug and standard therapy assessment periods (table V).

Discussion

The results of this small, descriptive and exploratory study showed that new formulation pancrelipase delayed-release capsules produced similar safety and tolerability results compared with standard therapy in children aged <7 years, adding to the data on the safety and efficacy reported in patients with CF aged ≥7 years.[25,26] No clinically meaningful differences were observed between the two treatments.

Although one patient taking study drug had a TEAE of diaper rash judged by the investigator to be possibly treatment related, it is unclear whether this was truly a related TEAE, given the high incidence of diaper rashes in this population and the minimal clinical experience and published literature on diaper rashes related to PERT. No serious TEAEs were recorded; no discontinuations occurred due to TEAEs and all TEAEs reported in this study were judged by the investigators as mild. The safety of PERT has been established over years of clinical experience

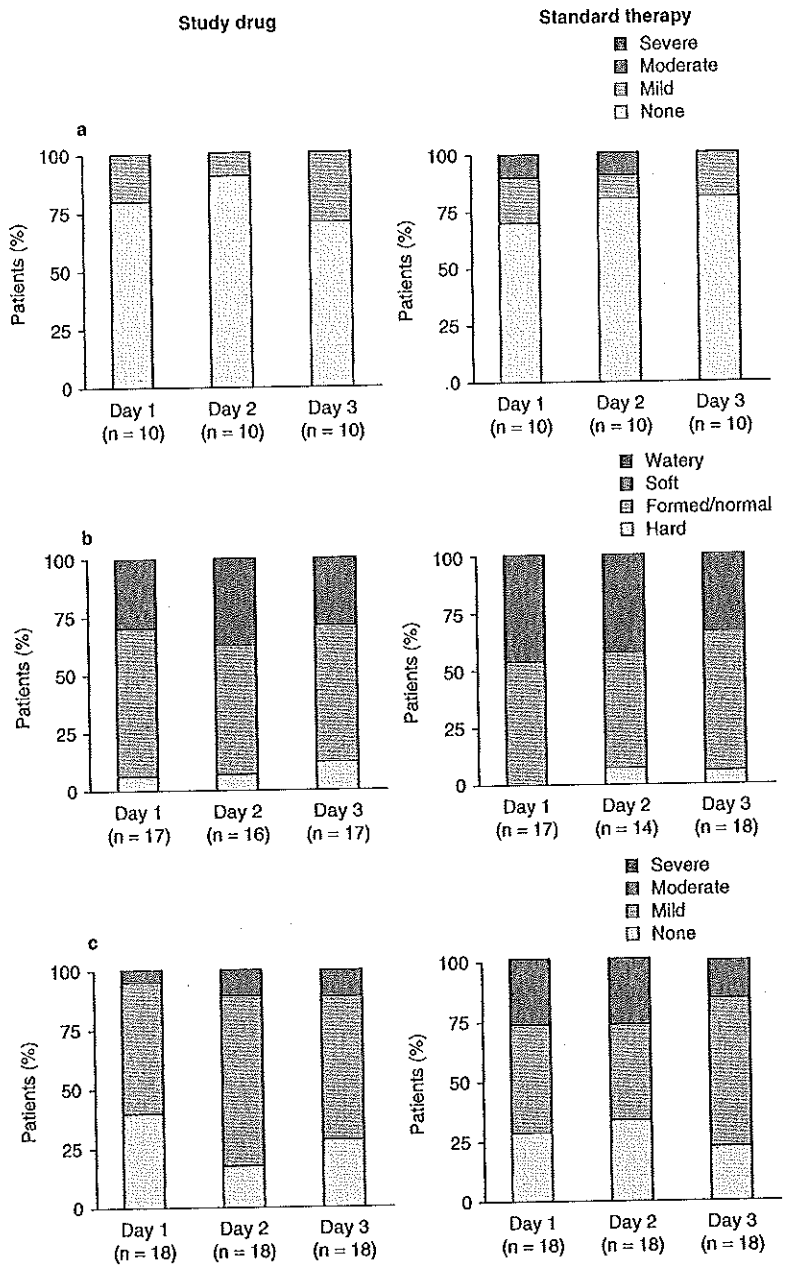

Fig. 2. Clinical symptom assessment [**(a)** abdominal pain, **(b)** stool consistency and **(c)** flatulence] for patients treated with study drug and standard therapy during the separate 3-day assessment periods.

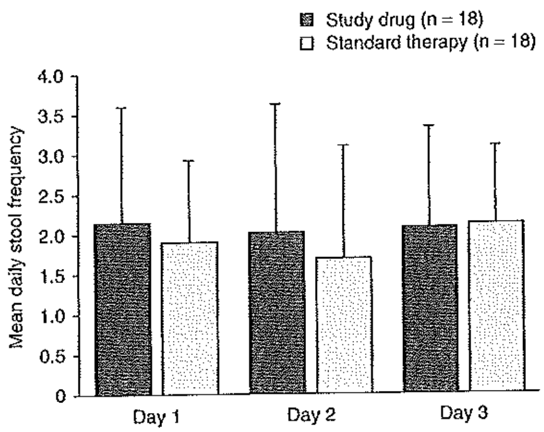

Fig. 3. Mean (SD) daily stool frequency for patients treated with study drug and standard therapy during the separate 3-day assessment periods.

and the results obtained from this short-term study do not suggest otherwise.

During the 3-day assessment period, the target dose was almost achieved for the study drug. No target dose was set for standard therapy as patients received their usual dose. The high variability in doses given limits the conclusions that can be drawn from comparing the dose received for study drug versus standard therapy. The calculated lipase dose was higher on the study drug compared with standard therapy. The new formulation study drug capsules are manufactured with a lipase activity at strictly 100% of the label claim; however, information regarding the level of potential under- or overfill in terms of lipase activity was not available for the standard therapy capsules. Thus, adherence to the recommended dose, which was based on consensus CF guidelines,[9,11] was confirmed in 15 of 18 patients receiving the study drug, but could not be confirmed while receiving standard therapy because the amount of overfill was unknown. This is of relevance to the concerns regarding the association of colonic strictures with high PERT doses. Adherence was high (78%) for study drug during the 3-day assessment period; however, mean overall adherence was close to 100% over the whole 12-day dispensing period. The study drug was no more difficult to dose accurately than standard therapy; in fact, the caregivers leaned slightly in favour of study drug for ease of accurate dosing, which is probably related to not having to divide up capsule contents.

The stool frequency and clinical symptom assessment data (abdominal pain, stool consistency and flatulence) showed that the study drug was clinically equivalent to standard therapy in terms of symptom control. Measurement of fat in spot stool samples indicated that faecal fat was relatively high during treatment with study drug and standard therapy, and there was no clinically meaningful difference between treatments; mean ± SD percent fat values of 28.1 ± 9.9 for the study drug and 27.9 ± 8.9 for standard therapy were recorded. These values are probably indicative for the paediatric CF population as a whole and, despite these data, most patients with CF grow relatively normally. Although there are no published data on how percent stool fat values relate to the commonly used outcome measure of coefficient of fat absorption (CFA), studies are being conducted that aim to explore the relationship between percent stool fat data and CFA. The high stool fat data may not be that surprising given that all infants have physiological fat malabsorption early in life, with a CFA ≥85% being normal for infants <6 months of age and the normal value for patients above this age

Table IV. Bodyweight and body mass index measured before and after study drug and standard therapy[a]

Variable	Study drug (n = 18)	Standard therapy (n = 18)
Bodyweight (kg)		
start of assessment	12.3 ± 4.5[b]	12.2 ± 4.6[c]
end of assessment	12.5 ± 4.5[d]	12.3 ± 4.5[b]
change[e]	0.1 ± 0.4	0.3 ± 0.4
BMI (kg/m^2)		
start of assessment	16.4 ± 1.4[b]	16.1 ± 1.5[c]
end of assessment	16.6 ± 1.6[d]	16.4 ± 1.4[b]
change[e]	0.3 ± 0.6	0.5 ± 0.7

a Values are expressed as mean ± SD.

b Measured at baseline.

c Measured at screening.

d Measured at end of treatment.

e Standard therapy duration (~21 days) was longer than study drug duration (10–14 days).

BMI = body mass index.

Table V. Summary of stool fat percentage, fat intake and total calorie intake measured during each separate 3-day assessment period[a]

Variable	Study drug (n = 18)	Standard therapy (n = 18)
Stool fat percentage	28.1 ± 9.9	27.9 ± 8.9
Fat intake (g)	46.6 ± 22.3	47.7 ± 26.4
Total calorie intake (kcal)	1239.7 ± 605.8	1272.0 ± 777.7

a Values are expressed as mean ± SD.

being ≥93%.[30] In addition, bodyweight was maintained in this short-term study, suggesting that use of both therapies results in enough caloric absorption to allow the maintenance of adequate nutritional status.

The safety and tolerability data from this study are consistent with those reported in a randomized study in patients with EPI due to CF aged 6–36 months[21] and an open-label study of patients with EPI due to CF aged <24 months;[20] however, both of these recently published studies investigated other formulations of pancrelipase. In terms of efficacy, these paediatric studies reported on-treatment mean CFA values in the range 77.8–84.7%.[20,21] However, these on-treatment mean CFA values are not at the normal levels expected for the non-CF population[31] and provide support for the recommendations for increased caloric requirements in the CF population. A recent open-label study[32] of a different porcine-derived PERT product, EUR-1008 (Zenpep™, Eurand SpA, Milan, Italy), in children aged <7 years with EPI due to CF showed a similar safety and tolerability profile to that observed in the current study. In addition, 11 out of 19 patients (58%) analysed in the aforementioned study by Wooldridge et al.[32] had no steatorrhoea or signs and symptoms of malabsorption when treated with PERT. Although the efficacy measures in that study were different, the conclusions drawn from it and the current study are similar and it is likely that the results are valid. However, a number of patients (8/19) in the study by Wooldridge et al.[32] still showed symptoms of EPI with PERT treatment. Based on clinical experience, some patients will not have resolution of significant steatorrhoea despite optimization of currently available PERT and acid-reducing agents.[33,34] Thus, there is a need for some people with CF who are adherent to diet recommendations to receive enteral nutritional supplementation, and a limited number will have low weight gain despite this support. Therefore, another possible reason for the relatively high stool fat may be imperfections in currently available therapy.

This was an exploratory open-label design study and the small sample size limits definitive conclusions. However, given the similar efficacy results for standard therapy and the study drug, it is likely there is not a large difference between the treatments. From a safety perspective, the sample size was too small to show any differences given the known favourable safety profile of PERT; this would probably be true even if the study had a randomized placebo-controlled design. Nevertheless, we believe these results are applicable to the wider paediatric CF population, particularly given the long history of use of these products in this population with beneficial results.

Conclusion

In this study, compared with standard therapy, the new formulation of pancrelipase delayed-release capsules had a similar safety and tolerability profile, was clinically comparable in terms of control of fat malabsorption and clinical symptoms, and was as easy to dose accurately in CF patients with EPI aged <7 years.

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References

1. Baker SS. Delayed release pancrelipase for the treatment of pancreatic exocrine insufficiency associated with cystic fibrosis. Ther Clin Risk Manag 2008; 4 (5): 1079-84
2. Borowitz D, Durie PR, Clarke LL, et al. Gastrointestinal outcomes and confounders in cystic fibrosis. J Pediatr Gastroenterol Nutr 2005; 41 (3): 273-85
3. Littlewood JM, Wolfe SP, Conway SP. Diagnosis and treatment of intestinal malabsorption in cystic fibrosis. Pediatr Pulmonol 2006; 41 (1): 35-49
4. DiMagno MJ, DiMagno EP. Chronic pancreatitis. Curr Opin Gastroenterol 2006; 22 (5): 487-97
5. Layer P, Holtmann G. Pancreatic enzymes in chronic pancreatitis. Int J Pancreatol 1994; 15 (1): 1-11
6. Abdel Aziz AM, Lehman GA. Current treatment options for chronic pancreatitis. Curr Treat Options Gastroenterol 2007; 10 (5): 355-68
7. Goodin B. Nutrition issues in cystic fibrosis. Pract Gastroenterol 2005; 29 (5): 76-94
8. Davis PB, Drumm M, Konstan MW. Cystic fibrosis. Am J Respir Crit Care Med 1996; 154 (5): 1229-56
9. Stallings VA, Stark LJ, Robinson KA, et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc 2008; 108 (5): 832-9
10. FitzSimmons SC, Burkhart GA, Borowitz D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med 1997; 336 (18): 1283-9
11. Borowitz DS, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. J Pediatr 1995; 127 (5): 681-4
12. DiMagno EP, Malagelada JR, Go VL, et al. Fate of orally ingested enzymes in pancreatic insufficiency: comparison of two dosage schedules. N Engl J Med 1977; 296 (23): 1318-22
13. Dutta SK, Rubin J, Harvey J. Comparative evaluation of the therapeutic efficacy of a pH-sensitive enteric coated pancreatic enzyme preparation with conventional pancreatic enzyme therapy in the treatment of exocrine pancreatic insufficiency. Gastroenterology 1983; 84 (3): 476-82
14. Halm U, Löser C, Löhr M, et al. A double-blind, randomized, multicentre, crossover study to prove equivalence of pancreatin minimicrospheres versus microspheres in exocrine pancreatic insufficiency. Aliment Pharmacol Ther 1999; 13 (7): 951-7
15. Meyer JH, Elashoff J, Porter-Fink V, et al. Human postprandial gastric emptying of 1–3-millimeter spheres. Gastroenterology 1988; 94 (6): 1315-25
16. Vyas H, Matthew DJ, Milla PJ. A comparison of enteric coated microspheres with enteric coated tablet pancreatic enzyme preparations in cystic fibrosis: a controlled study. Eur J Pediatr 1990; 149 (4): 241-3
17. Domínguez-Muñoz JE, Birckelbach U, Glasbrenner B, et al. Effect of oral pancreatic enzyme administration on digestive function in healthy subjects: comparison between two enzyme preparations. Aliment Pharmacol Ther 1997; 11 (2): 403-8
18. Stern RC, Eisenberg JD, Wagener JS, et al. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. Am J Gastroenterol 2000; 95 (8): 1932-8
19. Safdi M, Bekal PK, Martin S, et al. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. Pancreas 2006; 33 (2): 156-62
20. Colombo C, Fredella C, Russo MC, et al. Efficacy and tolerability of Creon for children in infants and toddlers with pancreatic exocrine insufficiency caused by cystic fibrosis: an open-label, single-arm, multicenter study. Pancreas 2009; 38 (6): 693-9
21. Munck A, Duhamel JF, Lamireau T, et al. Pancreatic enzyme replacement therapy for young cystic fibrosis patients. J Cyst Fibros 2009; 8 (1): 14-8
22. U.S. Food and Drug Administration. FDA requires pancreatic extract manufacturers to submit marketing applications, 2004 Apr 27 [online]. Available from URL: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108289.htm [Accessed 2010 Apr 13]
23. Solvay Pharmaceuticals Inc. CREON® (pancrelipase) capsules, delayed-release for oral use [US prescribing information]. Marietta (GA): Solvay Pharmaceuticals Inc., Apr 2009 [online]. Available from URL: http://www.creon-us.com/assets/pdf/Highlights%20of%20Prescribing%20Information.pdf [Accessed 2010 Apr 13]
24. Shlieout G, Koerner A, Sczesny F, et al. Pancrelipase delayed-release capsules (CREON®) zero-overfill formulation (to-be-marketed) is pharmaceutically comparable to the current formulation [abstract no. SP-27]. JPEN J Parenter Enteral Nutr 2009; 33 (3): 227-8. Plus poster presented at the American Society for Parenteral and Enteral Nutrition (ASPEN) Clinical Nutrition Week; 2009 Feb 1–4; New Orleans (LA)
25. Trapnell BC, Maguiness K, Graff GR, et al. Efficacy and safety of Creon® 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2009; 8 (6): 370-7
26. Graff GR, Maguiness K, McNamara J, et al. Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged 7–11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. Clin Ther 2010; 32 (1): 89-103
27. Korpi-Steiner NL, Ward JN, Kumar V, et al. Comparative analysis of fecal fat quantitation via nuclear magnetic resonance spectroscopy (^{1}H NMR) and gravimetry. Clin Chim Acta 2009; 400 (1-2): 33-6
28. Centers for Disease Control and Prevention. Z-score data files, 2009 Aug 4 [online]. Atlanta (GA): Centers for Disease Control and Prevention. Available from URL: http://www.cdc.gov/growthcharts/zscore.htm [Accessed 2010 Apr 13]
29. Centers for Disease Control and Prevention. BMI percentile calculator for child and teen [online]. Atlanta (GA): Centers for Disease Control and Prevention. Available from URL: http://apps.nccd.cdc.gov/dnpabmi/ [Accessed 2010 Apr 13]
30. Borowitz D, Robinson KA, Rosenfeld M, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of

infants with cystic fibrosis. J Pediatr 2009; 155 (6 Suppl.): S73-93

31. Borowitz D, Konstan MW, O'Rourke MS, et al. Coefficients of fat and nitrogen absorption in healthy subjects and individuals with cystic fibrosis. J Pediatr Pharmacol Ther 2007; 12: 47-52

32. Wooldridge JL, Heubi JE, Amaro-Galvez R, et al. EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency. J Cyst Fibros 2009; 8 (6): 405-17

33. Carroccio A, Pardo F, Montalto G, et al. Use of famotidine in severe exocrine pancreatic insufficiency with persistent maldigestion on enzymatic replacement therapy: a long-term study in cystic fibrosis. Dig Dis Sci 1992; 37 (9): 1441-6

34. Kalivianakis M, Minich DM, Bijleveld CM, et al. Fat malabsorption in cystic fibrosis patients receiving enzyme replacement therapy is due to impaired intestinal uptake of long-chain fatty acids. Am J Clin Nutr 1999; 69 (1): 127-34

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Brief Report

Efficacy and Tolerability of a New Formulation of Pancrelipase Delayed-Release Capsules in Children Aged 7 to 11 Years With Exocrine Pancreatic Insufficiency and Cystic Fibrosis: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Two-Period Crossover, Superiority Study

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ABSTRACT

Background: Pancreatic enzyme replacement therapy (PERT) is essential for maintaining adequate nutrition in children with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF). The US Food and Drug Administration regulations now require all PERT products to undergo clinical efficacy and safety studies before they can be considered for marketing approval.

Objective: This study was conducted to compare the efficacy of a new formulation of pancrelipase (pancreatin) delayed-release 12,000–lipase unit capsules with placebo in children with EPI due to CF.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled, 2-period crossover, superiority study of the new formulation of pancrelipase delayed-release 12,000–lipase unit capsules in children aged 7 to 11 years with CF and EPI. In each period, pancrelipase or identical placebo capsules were taken for 5 days. The primary outcome measure was the coefficient of fat absorption (CFA); secondary outcome measures were the coefficient of nitrogen absorption (CNA) and clinical symptoms. The latter were assessed based on patient-reported daily stool frequency, stool consistency (hard, formed/normal, soft, or watery), flatulence (none, mild, moderate, or severe), and abdominal pain (none, mild, moderate, or severe). Safety measures included vital signs, physical examinations, standard laboratory safety tests (hematology and biochemistry), and adverse events.

Results: Seventeen patients were randomized to treatment and 16 completed the study; 1 patient withdrew consent during the first treatment period and was not included in the efficacy analysis. Patients' median age was 8.0 years (range, 7–11 years); 12 patients (70.6%) were male. CFA values were significantly greater for pancrelipase compared with placebo, with least squares mean (SE) values of 82.8% (2.7%) and 47.4% (2.7%), respectively ($P < 0.001$). The results were similar for CNA, with mean values of 80.3% (3.2%) and 45.0% (3.2%) ($P < 0.001$). Pancrelipase treatment had significantly greater effects on CFA and CNA in patients with a placebo CFA ≤50% than in those with a placebo CFA >50% (both parameters, $P < 0.001$ and $P = 0.008$, respectively). Significant improvements in stool fat, weight, and nitrogen and a significant reduction in daily stool frequency were observed with pancrelipase compared

These data were presented in part at the 23rd Annual North American Cystic Fibrosis Conference; October 15–17, 2009; Minneapolis, Minnesota.

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with placebo (all, $P < 0.001$). Symptoms of EPI were less severe and remained relatively stable during pancrelipase treatment, but worsened slightly during receipt of placebo. Treatment-emergent adverse events were reported in 5 patients (29.4%) during receipt of pancrelipase and in 9 patients (56.3%) during receipt of placebo; these were predominantly gastrointestinal events. There were no discontinuations due to treatment-emergent adverse events and no serious adverse events.

Conclusions: In this study in children with EPI due to CF, the new formulation of pancrelipase delayed-release capsules was associated with improvements in CFA, CNA, stool properties, and EPI symptoms compared with placebo. Pancrelipase delayed-release capsules appeared to be well tolerated. ClinicalTrials.gov identifier: NCT00690820. (*Clin Ther.* 2010;32:89–103) © 2010 Excerpta Medica Inc.

Key words: coefficient of fat absorption, pancreatic enzyme replacement therapy, pancrelipase, pediatric, cystic fibrosis, exocrine pancreatic insufficiency.

INTRODUCTION

Exocrine pancreatic insufficiency (EPI) is defined as the lack of digestive enzymes secreted by the pancreas in association with diseases such as cystic fibrosis (CF)[1–3] and chronic pancreatitis.[4–6] EPI leads to maldigestion, with resultant malabsorption of fat, protein, and fat-soluble vitamins, and ultimately to malnutrition.[3] CF is the most common life-shortening genetic disease in white individuals,[7] affecting epithelial secretory tissues and resulting in pancreatic and pulmonary dysfunction.[1] Approximately 85% of persons diagnosed with CF also have EPI,[8,9] and the symptoms frequently begin in newborns and increase throughout infancy.[10]

Approximately 90% of patients with EPI due to CF are treated with pancreatic enzyme replacement therapy (PERT) to maintain adequate nutrition.[11] If EPI is left untreated, the subsequent malnutrition and debilitating symptoms (eg, steatorrhea, abdominal pain) may lead to poor growth, poor weight gain, and failure to thrive in children with CF.[9] PERT is particularly important for supporting nutrition, with the goal of achieving normal patterns of growth and development in children of all ages with EPI due to CF, and the maintenance of normal weight in adults.[12] Nutrition and lung function are closely linked in CF; poor nutrition as a result of EPI leads to reduced height and weight, which in turn leads to reduced lung function and, ultimately, an increase in mortality risk.[13,14] Well-nourished children are likely to exhibit more normal growth status, which is associated with better pulmonary function and improved outcomes.[12]

The efficacy and safety profile of PERT in patients with EPI has been evaluated in double-blind, placebo- and active-controlled studies, as well as in open-label studies.[15–21] Pancrelipase (pancreatin) delayed-release capsules, US Pharmacopeia,* have been used for >20 years to provide essential PERT for maldigestion due to EPI.

Since 2004, US Food and Drug Administration (FDA) regulations have required clinical efficacy and safety studies for the approval of all PERT products.[22] A new formulation of pancrelipase delayed-release capsules† has recently been approved by the FDA for the treatment of patients of all ages with EPI due to CF or other conditions. Approval of this formulation was based on a randomized, double-blind, placebo-controlled crossover study, which found that the new pancrelipase delayed-release 24,000–lipase unit capsules were superior to placebo in improving fat digestion in patients aged ≥12 years with EPI due to CF.[23] The pancrelipase capsule was associated with significantly higher coefficient of fat absorption (CFA) and coefficient of nitrogen absorption (CNA) values compared with placebo (CFA: 88.6 vs 49.6, respectively [$P < 0.001$]; CNA: 85.1 vs 49.9 [$P < 0.001$]). Clinical symptoms were decreased, and the formulation was well tolerated.

Two studies of the new formulation of pancrelipase in pediatric populations have recently been completed. This paper reports on one of them—a double-blind, placebo-controlled study of the efficacy and tolerability of the new pancrelipase delayed-release 12,000–lipase unit capsules in patients aged 7 to 11 years with EPI due to CF. Based on information in the manufacturer's clinical study database and the published literature, this is the first published study of the new formulation in children aged <12 years.

*Trademark: CREON® 5, 10, and 20 capsules (Solvay Pharmaceuticals, Inc., Marietta, Georgia).
†Trademark: CREON® 6000–, 12,000–, and 24,000–lipase unit capsules (Solvay Pharmaceuticals).

PATIENTS AND METHODS

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, 2-period crossover, superiority study in children with CF and EPI. The aim was to test the null hypothesis of no difference in the mean change from baseline in CFA between the new formulation of pancrelipase delayed-release 12,000–lipase unit capsules and placebo in patients with EPI due to CF.

The study was conducted at 10 centers across the United States between June 13, 2008, and December 1, 2008. It was conducted in compliance with the Good Clinical Practice guidelines and applicable national regulations.[24–27] The study was approved by the appropriate institutional review board/independent ethics committee for each site. Written informed consent was obtained from a parent or legally acceptable representative and informed assent was obtained from all patients before performance of any study-related procedures.

Patients

The study enrolled patients aged 7 to 11 years who had a confirmed diagnosis of CF and EPI. A confirmed diagnosis of CF was defined by the presence of clinical symptoms consistent with CF in addition to 2 positive sweat tests and/or 2 disease-causing mutations detected on CF transmembrane conductance regulator gene analysis. A confirmed diagnosis of EPI was defined as a CFA <70% without pancreatic enzyme supplementation or as human fecal elastase <50 µg/g stool, either measured within the past 12 months.

Patients must have been receiving treatment with a commercially available PERT product at a stable dose for >3 months. They had to be in clinically stable condition, without evidence of acute respiratory disease, for at least 1 month before enrollment. In addition, only patients with a stable body weight (defined as a decline of no more than 5% within 3 months of enrollment) were included. Patients had to be able to swallow capsules and to consume a standardized diet designed to provide sufficient fat to require a minimum of 12,000 lipase units of pancreatic enzyme supplementation per meal.

Patients were excluded if they had severe medical conditions that might limit participation in or completion of the study or if they had recently undergone major surgery (excluding appendectomy). Additional exclusions were a body mass index percentile for age of <10%; ileus or acute abdomen; malignancy of the digestive tract (excluding pancreatic cancer); HIV; celiac disease; Crohn's disease; known allergy to pancrelipase (pancreatin) or the inactive ingredients in pancrelipase delayed-release capsules; or exposure to an experimental drug within 30 days of the start of the study.

No intake of any oral enzyme preparation other than study medication was permitted during the 2 crossover treatment periods. Other concomitant medications prohibited during the crossover periods were nutritional supplements containing medium-chain triglycerides, narcotic analgesics, antidiarrheals, antispasmodics, and laxatives. Use of immunosuppressive drugs, excluding systemic steroids, was also prohibited. Concomitant medication affecting duodenal pH, acting on gastric emptying, or interfering with bile secretion was permitted, as long as the medication was commercially available and was prescribed at a dose within the recommended range.

Patients did not pay for testing or study visits. They received financial compensation for their time according to local institutional review board regulations.

Study Treatment

Each investigational site was supplied with blinded, packaged study medication. The active-treatment and placebo capsules were identical in appearance, shape, smell, and taste, and were packaged in the proper proportions to ensure the desired doses and maintenance of blinding.

Patients received pancrelipase 12,000–lipase unit capsules or identical placebo capsules. The number of capsules to be consumed was calculated to provide a target dose of 4000 lipase units/g of dietary fat intake, according to the upper limit recommended in CF consensus statements.[9,12,28] For example, if the meal plan included 94 g of fat daily, the number of capsules was calculated as 94 × 4000 = 376,000 total lipase units, divided by 12,000 = 31.3, or 31 capsules. To maintain normal nutrition, each patient received an individualized, prospectively designed diet containing ≥40% of calories derived from fat. Patients requiring a diet of 2000 kcal/d would need ~90 g of fat per day. As long as ≥40% of each patient's total calorie intake was derived from fat, no minimum daily dietary fat requirement was implemented.

Patients were evaluated for eligibility at visit 1 while continuing their usual PERT. Usual PERT was then continued for up to 14 days while eligibility was confirmed. At visit 2, which took place on day 1 of the first crossover period (baseline), patients were randomized to 1 of 2 treatment sequences—pancrelipase followed by placebo, or placebo followed by pancrelipase. Each treatment was taken for 5 days. Visit 3 took place at the end of the first crossover period (day 6 or 7) and included a physical examination, measurement of vital signs, and safety assessments. This visit was followed by a washout period of 3 to 14 days, during which patients received their previous PERT. Patients entered the second crossover period at visit 4. The procedures and timing of this period were identical to those of the first crossover period. Visit 5 marked the end of the second period and included a physical examination, measurement of vital signs, and safety assessments. A safety follow-up call was made 5 to 7 days after visit 5. During both crossover periods, patients stayed in a dedicated research facility, such as a US National Institutes of Health–funded General Clinical Research Center/Unit, and were allowed to return home during washout periods.

The randomization scheme was generated by the Global Clinical Supplies Office of Solvay Pharmaceuticals B.V., Weesp, The Netherlands. Patients were assigned to a treatment sequence via a centralized electronic interactive voice response system (IVRS). The IVRS was to be used if emergency unblinding was required as a result of an adverse event (AE); any attempt to unblind either treatment or patient was recorded, and specific individuals within Solvay Pharmaceuticals B.V. were notified of the attempt. Before any treatment code could be broken, the investigators were to determine the potential relationship between the AE and study treatment. A 24-hour telephone number was available in case there was a need for emergency unblinding of a treatment code and the investigator had no access to the unblinding procedures.

Efficacy Assessments

The primary efficacy outcome, CFA, was assessed by analyzing stool samples. To ensure accurate collection of stools derived from a known dietary intake, patients were administered two 250-mg doses of blue food dye (FD&C Blue #2 indigo carmine) 72 hours apart, marking the beginning and end of each stool collection period (days 2 and 5 of each crossover period). Stool collections were performed during each crossover period, beginning after the appearance of the first marker and ending with the stool containing the second marker.

Dietary recording took place during each treatment period. To accurately quantify the dietary intake of the prospectively designed diet, site staff monitored and maintained a record of patients' daily dietary intake. Food intake was quantified by weight. In addition, site staff assessed patients' gastrointestinal symptoms on every day of both crossover periods. Dietary intake of fat, protein, and calories was quantified by the site dietitian using food labels, the US Department of Agriculture national nutrient database, and appropriate nutrient analysis software (eg, Food Processor SQL version 10.0, Esha Research, Salem, Oregon). Compliance with dosing was recorded by site staff at each meal, and enzyme doses were recorded and checked for accuracy.

The CFA was calculated based on fat intake and excretion using the following equation: CFA (%) = 100 ([grams fat intake – grams fat excretion]/grams fat intake). Stool fat was measured in the stool samples collected between the 2 dye markers in both crossover periods. Total daily fat intake was determined according to each patient's dietary intake during both 72-hour stool-collection periods. Stool fat was determined by the gravimetric method.[29]

Secondary outcome measures included the CNA, calculated using the following equation: CNA (%) = 100 ([grams nitrogen intake – grams nitrogen excretion]/grams nitrogen intake). Stool nitrogen was assessed according to the method described by Kjeldahl.[30] Nitrogen intake was calculated based on the protein intake recorded in patients' dietary diaries during the two 72-hour stool-collection periods and evaluated using appropriate software.

Subanalyses were performed based on the severity of placebo EPI. The CFA and CNA data were compared in 2 subgroups: placebo CFA ≤50% and placebo CFA >50%.

For the assessment of clinical symptoms, the investigators asked patients to provide the following information: stool frequency (number per day); mean stool consistency (0 = hard, 1 = formed/normal, 2 = soft, and 3 = watery); mean flatulence (0 = none, 1 = mild, 2 = moderate, and 3 = severe); and mean abdominal pain (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The clinical global impression (CGI) of disease symptoms was rated by the investigator at all study visits using the following scale: 0 = none (symptoms not present); 1 = mild (symptoms present but not bothersome); 2 = moderate (symptoms bothersome); 3 = severe (symptoms interfered with normal activities); and 4 = incapacitating (symptoms prevented patient from continuing with normal activities).

Tolerability Assessments

Tolerability measures included vital signs, physical examinations, laboratory safety tests, and AEs. Physical examinations were performed at screening and at the end of each crossover period. Laboratory safety tests were performed during screening, at the end of the first crossover period, and at the beginning and end of the second crossover period. These tests included hematology (hemoglobin; hematocrit; red blood cell, white blood cell, and platelet counts; and differential blood count, if indicated) and biochemistry (glucose, creatinine, alkaline phosphatase, total bilirubin, conjugated bilirubin, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, uric acid, calcium, phosphate, and potassium). Urine pregnancy tests were performed in females of childbearing potential. Laboratory analyses using standard procedures were performed at Mayo Clinical Trial Services, Rochester, Minnesota. The investigators evaluated the clinical significance of laboratory values that were outside the normal range (or abnormal).

AEs were monitored from screening through the follow-up period. AEs were considered treatment emergent (TEAEs) if they began during treatment or if preexisting AEs worsened during treatment. The causal relationship between study drug and TEAEs was evaluated by the investigators as unrelated, unlikely to be related, possibly related, or probably related.

Statistical Methods

In this superiority study, a sample size of 16 was determined to have 95% power to detect an effect size of 1.0 using a paired t test with a 2-sided level of significance of 0.05. To account for dropouts, it was planned to randomize 18 patients (9 per treatment sequence).

All efficacy and tolerability variables were summarized using standard descriptive methods. The primary efficacy variable (CFA) was analyzed using ANOVA. The model included sequence, period, and treatment as fixed effects and patient-within-sequence as a random effect. From this model, an estimate of the treatment difference was derived, along with a 95% CI and P value for testing the null hypothesis H_0: $\mu_1 = \mu_2$, where μ_1 and μ_2 denote the population mean CFA for pancrelipase and placebo recipients, respectively. The null hypothesis was that the mean CFA for both treatment groups would be the same.

The primary analysis was performed on the full analysis sample, which included all randomized patients who received ≥1 dose of double-blind study medication and for whom ≥1 postbaseline assessment was available for any efficacy parameter. The safety sample was used for analysis of the tolerability data.

All analysis data sets and statistical outputs were produced using SAS version 8.2 or higher (SAS Institute Inc., Cary, North Carolina). Data were assessed graphically (box plots, normal probability plots, and residual-by-predicted plots) to confirm normality.

RESULTS

Of the 23 patients who provided consent, 17 were randomized to a treatment sequence (9 to pancrelipase then placebo, 8 to placebo then pancrelipase). Sixteen patients completed the study; 1 patient (pancrelipase/placebo sequence) withdrew consent on day 2 of the first treatment period (**Figure 1**). At screening, the pancreatic elastase value for all patients was 7.5 µg/g stool, with the exception of 1 patient, who had a pancreatic elastase value of 22 µg/g stool. There was a slight gender imbalance between treatment sequences, with 5 males (55.6%) receiving pancrelipase/placebo and 7 males (87.5%) receiving placebo/pancrelipase (**Table I**). There were no differences in any other demographic variables between treatment sequences. Four patients in the pancrelipase/placebo sequence took permitted acid-suppressing medication (proton-pump inhibitors [omeprazole, lansoprazole] or a histamine$_2$-receptor antagonist [ranitidine]) during the study. No patients in the placebo/pancrelipase sequence took acid-suppressing medication.

During pancrelipase treatment, the mean (SD) daily lipase dose was 4472 (743) units/g of fat consumed (16,941 [3602] units/kg body weight). The mean duration of exposure was 4.9 (0.8) days for pancrelipase and 5.1 (0.3) days for placebo. Adherence was 100% for both treatment sequences.

Efficacy

The least squares (LS) mean (SE) CFA values for pancrelipase and placebo were 82.8% (2.7%) and

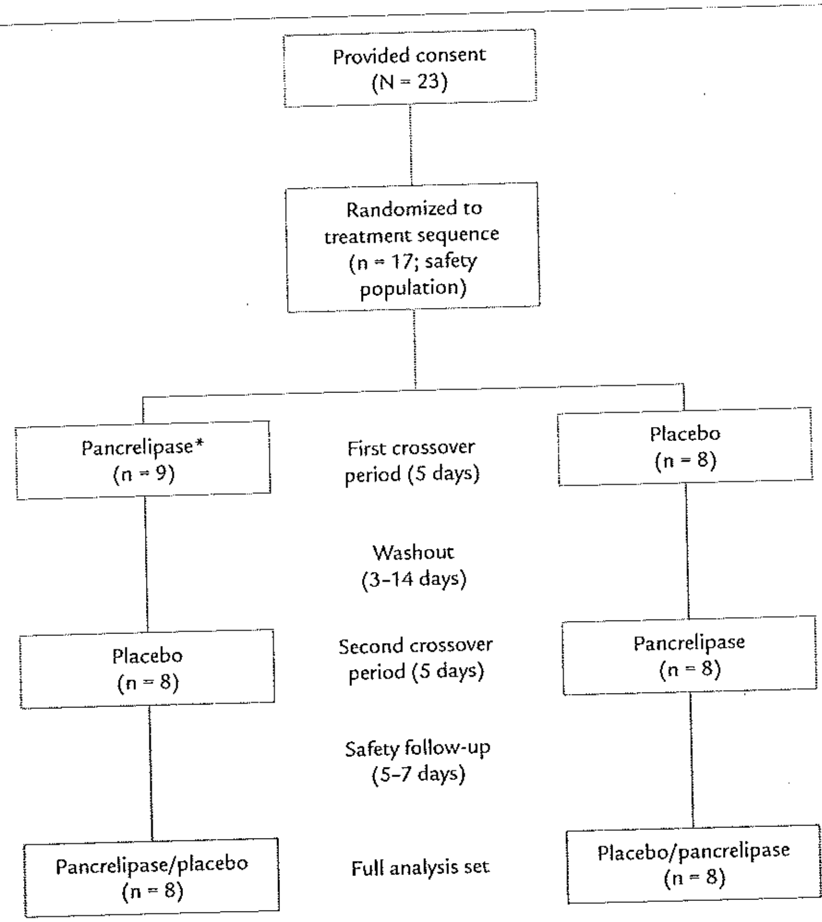

Figure 1. Study design and patient disposition. *One patient in the pancrelipase/placebo sequence withdrew consent on day 2 of the first treatment period and was not included in the efficacy analysis.

47.4% (2.7%), respectively, for a treatment difference of 35.4% ($P < 0.001$) (Table II). In the subgroup analysis of CFA data by the severity of placebo EPI, which is illustrated in Figure 2, the treatment difference was significantly greater in the subgroup with a placebo CFA ≤50% (44.5% [2.4%]; $P < 0.001$) than in the subgroup with a placebo CFA >50% (20.2% [4.1%]; $P = 0.008$) (Table II). All patients in the subgroup with a placebo CFA ≤50% had an increase in CFA of ≥30% during pancrelipase treatment.

The results for the CNA were similar to those for the CFA. The LS mean (SE) CNA values for pancrelipase and placebo were 80.3% (3.2%) and 45.0% (3.2%) ($P < 0.001$), respectively, for a treatment difference of 35.3% ($P < 0.001$) (Table III). In the subgroup analysis of CNA data by the severity of placebo EPI, the treatment difference was significantly greater in the subgroup with a placebo CFA ≤50% (45.2% [4.3%]; $P < 0.001$) than in the subgroup with a placebo CFA >50% (18.9% [3.8%]; $P = 0.008$).

CFA and CNA data for individual patients are illustrated in Figure 3. In general, the observed improvements in CFA and CNA in individual patients were of similar magnitude during pancrelipase treatment.

Although statistical significance was not tested, total fat and nitrogen intake on days 3 to 5 of each crossover period were similar for pancrelipase and for placebo. The mean (SD) fat intake was 338.3 (59.8) and

Table I. Patient characteristics at baseline, by treatment sequence.*

Variable	Pancrelipase/Placebo (n = 9)	Placebo/Pancrelipase (n = 8)	Total (N = 17)
Age, median (range), y	8.0 (7–11)	8.5 (8–11)	8.0 (7–11)
Sex, no. (%)			
Male	5 (55.6)	7 (87.5)	12 (70.6)
Female	4 (44.4)	1 (12.5)	5 (29.4)
White race, no.	9	8	17
CFA category during receipt of placebo (n = 8 per group), no. (%)			
≤50%	5 (62.5)	5 (62.5)	10 (62.5)
>50%	3 (37.5)	3 (37.5)	6 (37.5)
Height, mean (SD), m	1.3 (0.1)	1.4 (0.1)	1.3 (0.1)
Weight, mean (SD), kg	28.1 (7.0)	32.0 (8.9)	30.0 (7.9)
BMI, mean (SD), kg/m^2	16.3 (2.4)	17.3 (2.9)	16.8 (2.6)

CFA = coefficient of fat absorption; BMI = body mass index.
*One patient in the pancrelipase/placebo sequence withdrew consent on day 2 of the first treatment period and was not included in the efficacy analysis.

Table II. Coefficient of fat absorption (CFA) results, by treatment and severity of exocrine pancreatic insufficiency (EPI).*

Variable	Pancrelipase (n = 16)	Placebo (n = 16)	Treatment Difference (Pancrelipase – Placebo) (n = 16)	P
CFA, %				
LS mean (SE)	82.8 (2.7)	47.4 (2.7)	35.4 (3.8)	<0.001
95% CI	77.0–88.6	41.6–53.2	27.2–43.6	–
CFA by severity of EPI, %				
Placebo CFA ≤50%	n = 10	n = 10	n = 10	
LS mean (SE)	81.8 (1.7)	37.3 (1.7)	44.5 (2.4)	<0.001
95% CI	77.9–85.7	33.4–41.2	39.0–50.0	–
Placebo CFA >50%	n = 6	n = 6	n = 6	
LS mean (SE)	84.5 (2.9)	64.3 (2.9)	20.2 (4.1)	0.008
95% CI	76.5–92.5	55.3–72.3	8.9–31.6	–

LS = least squares.
*One patient in the pancrelipase/placebo sequence withdrew consent on day 2 of the first treatment period and was not included in the efficacy analysis.

346.6 (53.1) g, respectively, and the mean nitrogen intake was 44.6 (20.2) and 45.3 (18.6) g.

All stool characteristics were significantly improved and stool frequency was significantly reduced with pancrelipase compared with placebo (all, $P < 0.001$) (Table IV). The symptoms of EPI (abdominal pain, flatulence, and stool consistency) were less severe during receipt of pancrelipase compared with placebo. Patients' symptoms remained relatively stable during pancrelipase treatment, whereas they worsened slightly during receipt of placebo (Figure 4). Investigators' CGI assessments reflected stabilization of the condi-

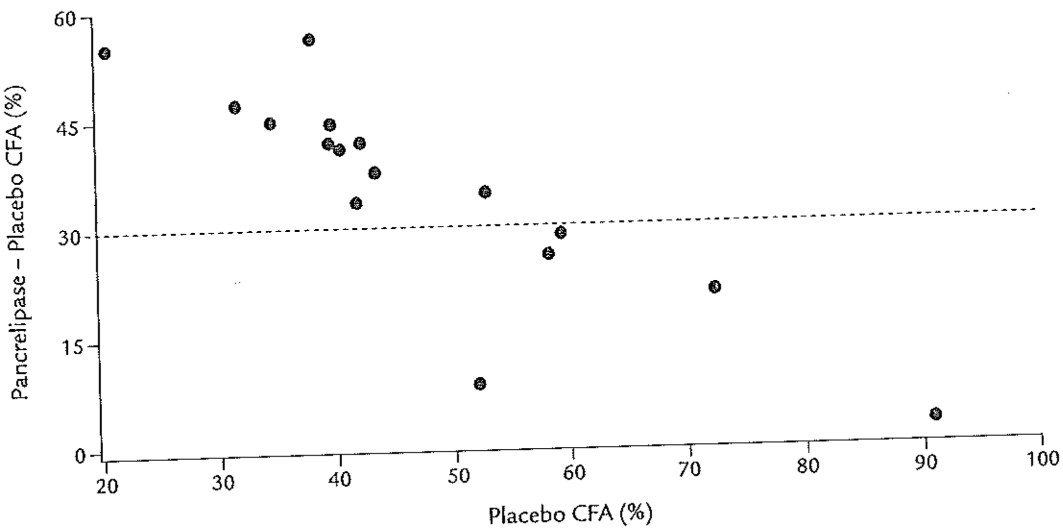

Figure 2. Individual patient data for the treatment difference (pancrelipase – placebo) in coefficient of fat absorption (CFA), by severity of exocrine pancreatic insufficiency (placebo CFA ≤50% or >50%). The dotted line indicates a 30% treatment difference in CFA.

Table III. Coefficient of nitrogen absorption (CNA) results, by treatment and severity of exocrine pancreatic insufficiency (EPI).*

Variable	Pancrelipase (n = 16)	Placebo (n = 16)	Treatment Difference (Pancrelipase – Placebo) (n = 16)	*P*
CNA, %				
LS mean (SE)	80.3 (3.2)	45.0 (3.2)	35.3 (4.5)	<0.001
95% CI	73.5–87.2	38.2–51.8	25.7–45.0	–
CNA by severity of EPI, %				
Placebo CFA ≤50%	n = 10	n = 10	n = 10	
LS mean (SE)	79.8 (3.1)	34.6 (3.1)	45.2 (4.3)	<0.001
95% CI	72.7–86.9	27.5–41.7	35.2–55.2	–
Placebo CFA >50%	n = 6	n = 6	n = 6	
LS mean (SE)	81.2 (2.7)	62.3 (2.7)	18.9 (3.8)	0.008
95% CI	73.7–88.7	54.8–69.8	8.3–29.5	–

LS = least squares; CFA = coefficient of fat absorption.
*One patient in the pancrelipase/placebo sequence withdrew consent on day 2 of the first treatment period and was not included in the efficacy analysis.

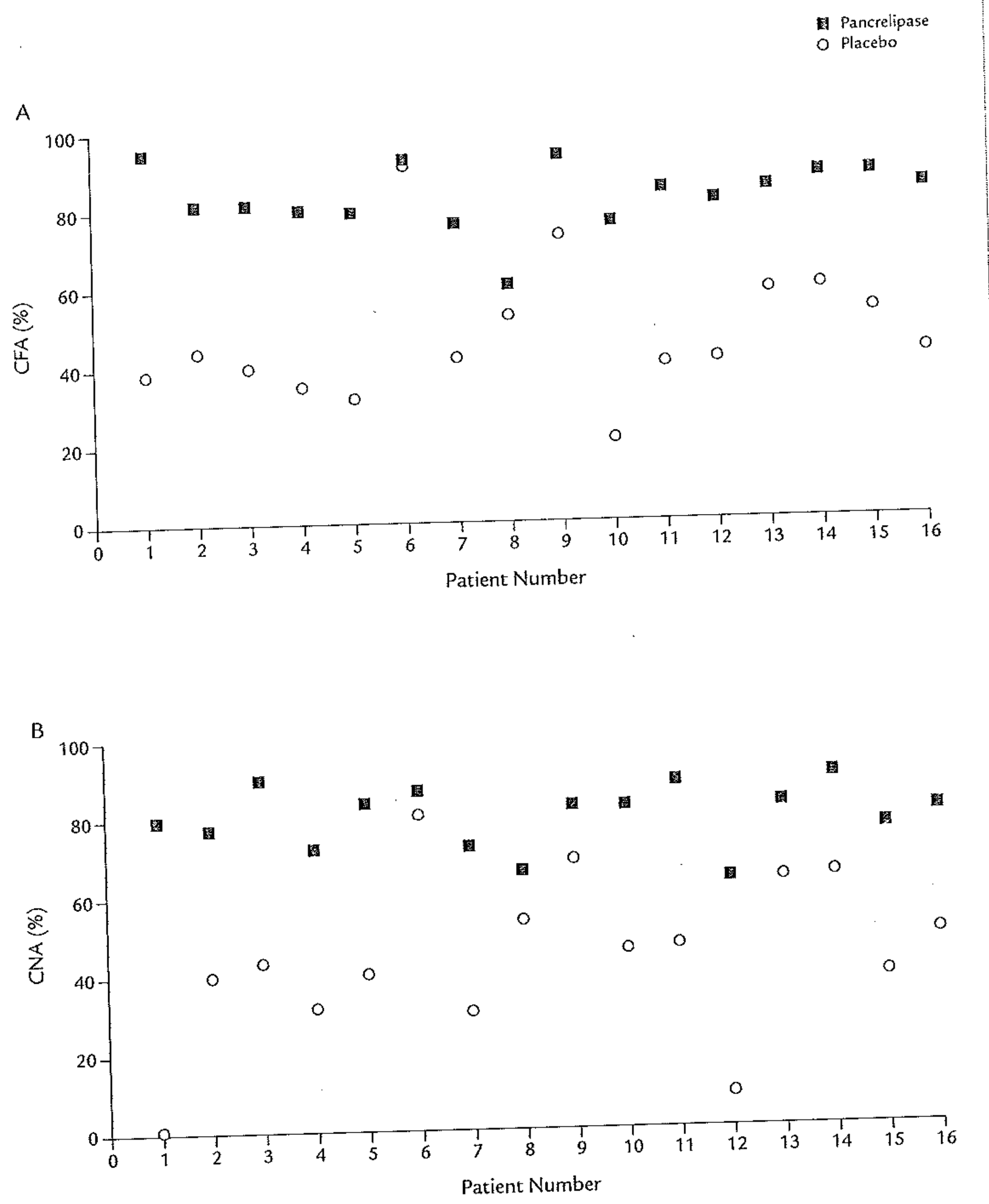

Figure 3. Individual patient data for (A) coefficient of fat absorption (CFA) and (B) coefficient of nitrogen absorption (CNA) with pancrelipase and placebo.

Table IV. Stool characteristics and frequency.* Data are least squares mean (SE).

Variable†	Pancrelipase (n = 16)	Placebo (n = 16)	Treatment Difference (Pancrelipase – Placebo) (n = 16)	P
Stool fat, g	58.1 (10.1)	182.9 (10.1)	-124.8 (14.3)	<0.001
Stool weight, g	165.9 (27.8)‡	436.3 (33.3)§	-270.4 (43.4)§	<0.001
Stool nitrogen, g	8.0 (1.8)	24.0 (1.8)	-15.9 (2.5)	<0.001
Daily stool frequency	1.9 (0.2)‖	3.4 (0.2)	-1.5 (0.3)	<0.001

*One patient in the pancrelipase/placebo sequence withdrew consent on day 2 of the first treatment period and was not included in the efficacy analysis.
†Stool fat, stool weight, and stool nitrogen were determined from stools obtained during the 72-hour collection period. Daily stool frequency was recorded in patient diaries each evening during both crossover treatment periods.
‡n = 12 (stool weight analyses not carried out in all patients).
§n = 10 (stool weight analyses not carried out in all patients).
‖n = 17.

tion during pancrelipase treatment, with no meaningful changes from the start to the end of the treatment period; in contrast, symptoms were assessed as having worsened during receipt of placebo (Figure 5).

Tolerability

TEAEs (predominantly gastrointestinal events) were reported in 5 patients (29.4%) during pancrelipase treatment and in 9 patients (56.3%) during receipt of placebo (Table V). As expected, gastrointestinal TEAEs were more prevalent during receipt of placebo (7 [43.8%]) than during receipt of pancrelipase (3 [17.6%]). No TEAEs were considered related to pancrelipase treatment, whereas 4 patients (25.0%) had TEAEs considered related to placebo (diarrhea, flatulence, abdominal pain, frequent bowel movements, weight decrease, and rash). No patients discontinued treatment due to a TEAE, and no serious TEAEs were reported. No clinically relevant treatment differences in laboratory parameters or vital signs were noted.

DISCUSSION

The results of this study of the new formulation of pancrelipase delayed-release 12,000–lipase unit capsules in children aged 7 to 11 years suggest that the new formulation was effective, with a favorable safety profile. The primary outcome variable, CFA, was significantly increased during receipt of pancrelipase treatment compared with placebo ($P < 0.001$). These data are consistent with the results of a similarly designed study in patients aged ≥12 years.[23] The individual CFA values obtained during the present study suggest that patients generally responded to pancrelipase treatment. More severe disease, as manifested by a placebo CFA ≤50%, was associated with greater improvements in CFA and CNA. Furthermore, fat and nitrogen absorption (CFA and CNA) during receipt of pancrelipase in this study were generally comparable to those reported for healthy adults (mean CFA, 93.5%; mean CNA, 88.1%).[31]

Results for the secondary outcome measures also indicated improvements with pancrelipase compared with placebo. For example, absorption of nitrogen (CNA), a marker of protein absorption, was significantly greater in patients during receipt of pancrelipase compared with placebo ($P < 0.001$). As was observed for CFA, patients with more severe disease had greater improvements in CNA while receiving pancrelipase. Mean stool fat, stool nitrogen, and stool weight were significantly lower during pancrelipase treatment compared with placebo (all, $P < 0.001$), whereas daily fat and nitrogen intake appeared to be similar for both pancrelipase and placebo (statistical significance not tested). The mean stool frequency was significantly reduced (by 1.5 stools per day) with pancrelipase compared with placebo ($P < 0.001$). Reduced stool frequency, along with improvement in other

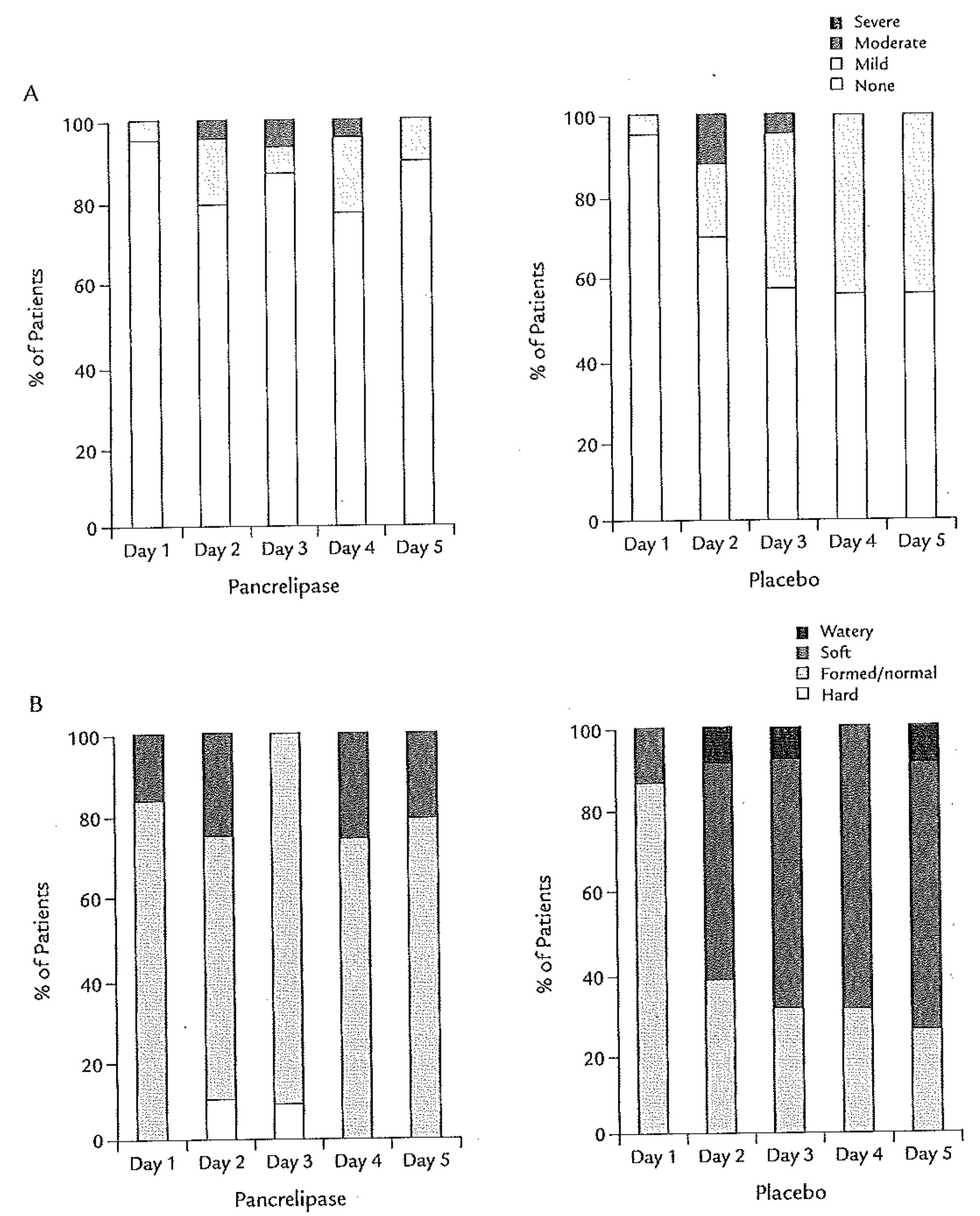

Figure 4. Effects of pancrelipase and placebo on clinical symptoms of exocrine pancreatic insufficiency: (A) abdominal pain; and (B) stool consistency.

(continued)

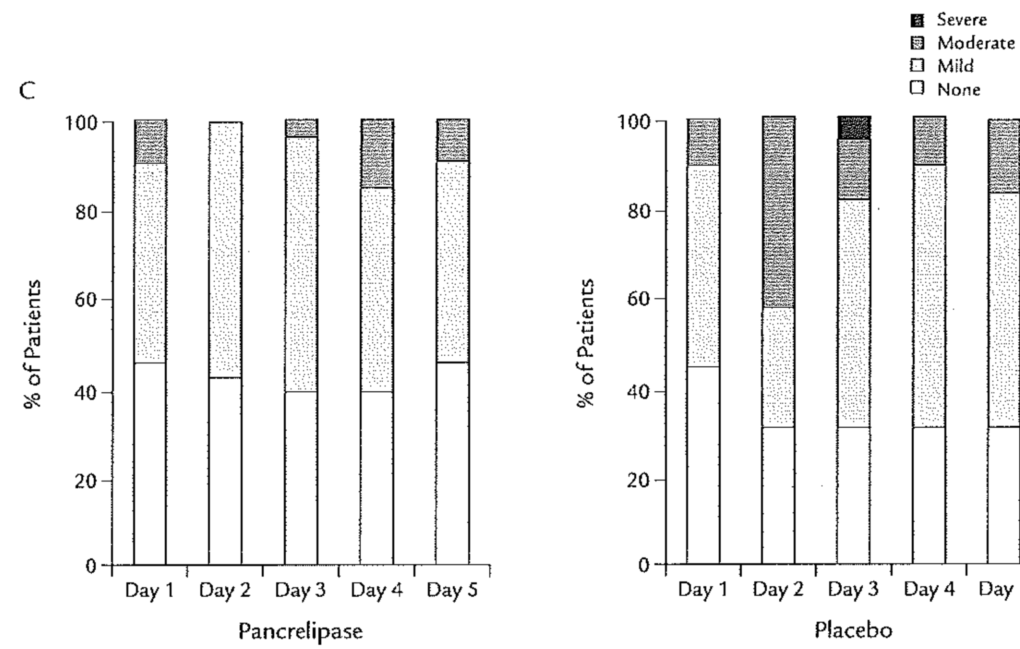

Figure 4 (continued). Effects of pancrelipase and placebo on clinical symptoms of exocrine pancreatic insufficiency: (C) flatulence.

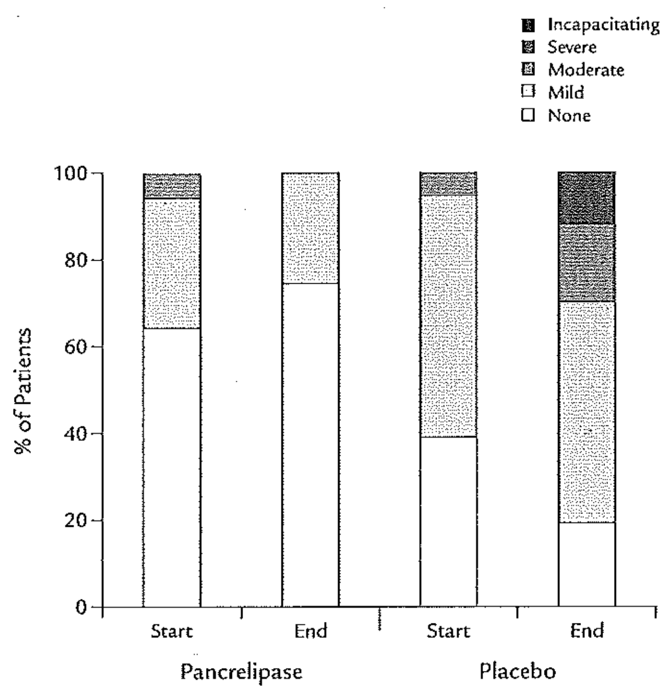

Figure 5. Investigators' clinical global impression of disease severity.

Table V. Treatment-emergent adverse events (TEAEs), using Medical Dictionary for Regulatory Activities (version 8.1) terms. Data are number (%) of patients.

Variable	Pancrelipase (n = 17)	Placebo (n = 16)
Any TEAE	5 (29.4)	9 (56.3)
Serious TEAEs	0	0
Discontinuation due to TEAEs	0	0
Severe TEAEs	0	0
Treatment-related TEAEs	0	4 (25.0)
Gastrointestinal disorders	3 (17.6)	7 (43.8)
Rectal discharge	0	1 (6.3)
Diarrhea	0	2 (12.5)
Increased fecal volume	0	1 (6.3)
Flatulence	0	2 (12.5)
Abdominal pain	1 (5.9)	4 (25.0)
Frequent bowel movements	0	1 (6.3)
Nausea	0	1 (6.3)
Vomiting	2 (11.8)	0
Investigations	1 (5.9)	2 (12.5)
Blood glucose increased	1 (5.9)	1 (6.3)
Weight decreased	0	1 (6.3)
Nervous system disorders	2 (11.8)	1 (6.3)
Headache	2 (11.8)	0
Dizziness	0	1 (6.3)
Skin and subcutaneous tissue disorders	1 (5.9)	3 (18.8)
Cold sweat	0	1 (6.3)
Rash	0	1 (6.3)
Rash, macular	0	1 (6.3)
Urticaria	1 (5.9)	0

stool and symptom measures, may have a positive effect on quality of life, although this was not evaluated in the present study.

From days 1 through 5 of both crossover periods, clinical symptoms (abdominal pain, stool consistency, and flatulence) remained stable with pancrelipase and worsened slightly with placebo. When considering these results, it should be noted that some of the younger children in this study may have had limited ability to assess the intensity of their symptoms accurately. Investigator-assessed CGI indicated worsening with placebo and no significant change with pancrelipase.

Pancrelipase delayed-release capsules appeared to be well tolerated in this study. There were no discontinuations due to TEAEs, and the incidence of TEAEs was lower during pancrelipase treatment compared with placebo.

The mean CFA and CNA values for pancrelipase in this study (82.8% and 80.3%, respectively) are comparable to those from previous clinical studies of PERT in patients with CF. For example, in the studies of different pancrelipase formulations by Stern et al[21] (18 patients aged 7–18 years receiving pancrelipase) and Colombo et al[32] (12 patients aged 1–24 months receiving pancrelipase), the mean CFA values were 84.1% and 84.7%, respectively. In a study of pancrelipase 24,000–lipase unit capsules (same formulation as in the present trial) in patients aged ≥12 years (median age, 22 years), Trapnell et al[23] reported a CFA of 88.6% and a CNA of 85.1%. The slightly lower CFA in the present study may be attributable to the high amount of fat calories ingested by patients.

In this study in CF patients aged 7 to 11 years, the treatment benefit in terms of the mean treatment difference in CFA between pancrelipase and placebo (35.4%; $P < 0.001$) was consistent with that reported in other trials. The treatment difference was 31.6% in the patients aged 7 to 18 years studied by Stern et al[21] ($P < 0.001$) and 39.0% in the older patients studied by Trapnell et al[23] ($P < 0.001$). Comparison of the data from these studies suggests that treatment differences are independent of age; however, it is not possible to draw any firm conclusions, given the limited age range investigated in the present study.

Similar efficacy has also been reported for other porcine-derived PERT products. For example, in a placebo-controlled study of a different PERT formulation in patients aged 8 to 36 years with CF, on-PERT mean CFA and CNA values were 79.4% and 83.8%, respectively.[15] In a prospective, randomized study of a high-buffered PERT formulation in CF patients aged 12 to 28 years, the on-PERT mean CFA value was 81.8%.[18] In an open-label Phase I study of a nonporcine, microbial-derived PERT product in patients with CF, the observed CFA and CNA values (69.7% and 74.6%, respectively) were lower than those in the present study, as well as in other studies of porcine-derived PERT,[15,18,21,23,32] although the greatest clinical improvements were seen in those with baseline CFA and CNA values <40%,[16] consistent with observations in the present study.

The tolerability data from the present study are consistent with previous studies of pancrelipase in patients with CF. In the present study, TEAEs occurred in 29.4% of patients receiving pancrelipase and 56.3% of patients receiving placebo, and no serious TEAEs were reported. A similar safety profile was observed in other placebo-controlled studies, in which the incidence of TEAEs was generally lower with pancrelipase than with placebo and there were no serious treatment-related TEAEs.[21,23,33] As in previous studies, the majority of TEAEs in this study were judged unrelated to treatment and consistent with the underlying disease.

Although this study included only a small number of patients, the sample size was deemed sufficient to obtain clinically and statistically significant data regarding efficacy in this patient population. The main limitation of this study was the restricted age range; further studies are required to confirm the efficacy of the new formulation of pancrelipase in the younger population with CF. A study investigating the new formulation of pancrelipase in patients aged <7 years was recently completed but has yet to be reported. Although the low incidence of TEAEs in the present study was encouraging, and previous clinical studies and substantial clinical experience with pancrelipase suggest a favorable safety profile in younger patients with CF, a long-term study would be required to fully evaluate AEs, clinical symptoms, and tolerability over time. The short duration of the present study was necessary owing to the inclusion of a placebo arm.

CONCLUSIONS

In these children aged 7 to 11 years with EPI due to CF, the new formulation of pancrelipase delayed-release 12,000–lipase unit capsules significantly improved fat absorption, as measured by the CFA, compared with placebo. The new formulation appeared to be well tolerated.

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REFERENCES

1. Baker SS. Delayed release pancrelipase for the treatment of pancreatic exocrine insufficiency associated with cystic fibrosis. *Ther Clin Risk Manag.* 2008;4:1079–1084.
2. Borowitz D, Durie PR, Clarke LL, et al. Gastrointestinal outcomes and confounders in cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 2005;41:273–285.
3. Littlewood JM, Wolfe SP, Conway SP. Diagnosis and treatment of intestinal malabsorption in cystic fibrosis. *Pediatr Pulmonol.* 2006;41:35–49.
4. DiMagno MJ, DiMagno EP. Chronic pancreatitis. *Curr Opin Gastroenterol.* 2006;22:487–497.
5. Layer P, Holtmann G. Pancreatic enzymes in chronic pancreatitis. *Int J Pancreatol.* 1994;15:1–11.
6. Abdel Aziz AM, Lehman GA. Current treatment options for chronic pancreatitis. *Curr Treat Options Gastroenterol.* 2007;10:355–368.
7. Ratjen F, Döring G. Cystic fibrosis. *Lancet.* 2003;361: 681–689.
8. Couper RT, Corey M, Moore DJ, et al. Decline of exocrine pancreatic function in cystic fibrosis patients with pancreatic sufficiency. *Pediatr Res.* 1992;32:179–182.
9. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 2002;35:246–259.
10. Bronstein MN, Sokol RJ, Abman SH, et al. Pancreatic insufficiency, growth, and nutrition in infants identified by newborn screening as having cystic fibrosis. *J Pediatr.* 1992;120:533–540.

11. FitzSimmons SC. The changing epidemiology of cystic fibrosis. *J Pediatr.* 1993;122:1-9.
12. Stallings VA, Stark LJ, Robinson KA, et al, for the Ad Hoc Working Group. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: Results of a systematic review. *J Am Diet Assoc.* 2008;108: 832-839.
13. Konstan MW, Butler SM, Wohl ME, et al, for the Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr.* 2003;142:624-630.
14. Beker LT, Russek-Cohen E, Fink RJ. Stature as a prognostic factor in cystic fibrosis survival. *J Am Diet Assoc.* 2001;101:438-442.
15. Konstan MW, Stern RC, Trout JR, et al. Ultrase MT12 and Ultrase MT20 in the treatment of exocrine pancreatic insufficiency in cystic fibrosis: Safety and efficacy. *Aliment Pharmacol Ther.* 2004;20:1365-1371.
16. Borowitz D, Goss CH, Limauro S, et al. Study of a novel pancreatic enzyme replacement therapy in pancreatic insufficient subjects with cystic fibrosis. *J Pediatr.* 2006;149: 658-662.
17. Borowitz D, Goss CH, Stevens C, et al. Safety and preliminary clinical activity of a novel pancreatic enzyme preparation in pancreatic insufficient cystic fibrosis patients. *Pancreas.* 2006;32:258-263.
18. Brady MS, Garson JL, Krug SK, et al. An enteric-coated high-buffered pancrelipase reduces steatorrhea in patients with cystic fibrosis: A prospective, randomized study. *J Am Diet Assoc.* 2006;106:1181-1186.
19. Safdi M, Bekal PK, Martin S, et al. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: A multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis [published correction appears in *Pancreas.* 2007;34:174]. *Pancreas.* 2006;33:156-162.
20. Santini B, Antonelli M, Battistini A, et al. Comparison of two enteric coated microsphere preparations in the treatment of pancreatic exocrine insufficiency caused by cystic fibrosis. *Dig Liver Dis.* 2000;32:406-411.
21. Stern RC, Eisenberg JD, Wagener JS, et al. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. *Am J Gastroenterol.* 2000;95: 1932-1938.
22. US Food and Drug Administration. FDA requires pancreatic extract manufacturers to submit marketing applications. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108289.htm. Accessed December 2, 2009.
23. Trapnell BC, Maguiness K, Graff GR, et al. Efficacy and safety of Creon 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. *J Cyst Fibros.* 2009;8: 370-377.
24. Code of Federal Regulations. Title 21—Food and Drugs. http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Accessed December, 2, 2009.
25. International Conference on Harmonisation. Guideline for Industry. Structure and contents of clinical study reports (ICH E3). http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf. Accessed December 14, 2009.
26. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials (E9). http://www.ich.org/LOB/media/MEDIA485.pdf. Accessed December 14, 2009.
27. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Guideline for good clinical practice E6(R1). http://www.ich.org/LOB/media/MEDIA482.pdf. Accessed December 14, 2009.
28. Sinaasappel M, Stern M, Littlewood J, et al. Nutrition in patients with cystic fibrosis: A European Consensus. *J Cyst Fibros.* 2002;1:51-75.
29. Van De Kamer JH, Ten Bokkel Huinink H, Weyers HA. Rapid method for the determination of fat in feces. *J Biol Chem.* 1949;177:347-355.
30. Kjeldahl J. A new method for the determination of nitrogen in organic matter. *Z Anal Chem.* 1883;22: 366-382.
31. Borowitz D, Konstan MW, O'Rourke MW, et al. Coefficients of fat and nitrogen absorption in healthy subjects and individuals with cystic fibrosis. *J Pediatr Phamacol Ther.* 2007; 12:47-52.
32. Colombo C, Fredella C, Russo MC, et al. Efficacy and tolerability of Creon for Children in infants and toddlers with pancreatic exocrine insufficiency caused by cystic fibrosis: An open-label, single-arm, multicenterstudy. *Pancreas.* 2009;38:693-699.
33. Sander-Struckmeier S, Boyd D, Caras SD. CREON: Efficacy and safety in children less than 7 years old with exocrine pancreatic insufficiency due to cystic fibrosis. *J Cyst Fibros.* 2009; 8(Suppl 2):S80. Abstract P324.

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